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A Journal of Neurology

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MARCH, 1942

BRAIN

VOL. 65, PART 1.

STRUCTURE OF THE NEUROHYPOPHYSIS WITH SPECIAL REFERENCE TO NERVE ENDINGS.

BY E. VAZQUEZ-LOPEZ.
(Imperial Cancer Research Fund, Mill Hill, London, N.W.7.)

THE essential structural elements of the neurohypophysis have now been known for close on fifty years. Since their discovery they have formed the subject of many published papers, but the attention of each successive author has been focused upon some particular element; nerve fibres, for instance, which he has studied as if it constituted an isolated system rather than one of a series of inter-related systems—as if *any* single system could have independent anatomical and functional value. The result has been that, since the manner of the architectural integration of the different structural elements has remained practically unknown, no clearly synthesized picture of the organ as a whole has been attained, reasoning from structure to function has been all but impossible, and investigations of the part which the neurohypophysis plays in the animal economy have been severely handicapped. The main purpose of the present paper is to describe and discuss the manner in which nerve fibres end in the neurohypophysis—a subject of which almost nothing has been known hitherto —and here again in this investigation the prevailing lack of knowledge of microscopical architecture has been severely felt. Adequate study of nerve endings has necessitated a fairly comprehensive investigation of how the various essential structural elements are arranged in the organ, for without such information it is impossible to perceive significant relationships of the nerve endings and difficult to suggest their probable functional rôle. It will be appreciated that under these circumstances some account of the more general findings must of necessity form the background of the present paper.

Material and Methods.

In the studies to be described here only normal pituitary bodies have been used. That of the horse has been found a material of choice both on account of its large size and because of the relatively simple arrangement of its elemental constituents. Pituitary bodies of ox, sheep, rabbit, guinea-pig and rat have also been studied, but will be referred to only in so far as some peculiarity in structure may help to a better understanding of the horse pituitary body in particular or of pituitary bodies in general.

Frozen sections have been used throughout and all staining has been by one or other of the silver and gold impregnation methods of the Spanish school. Thus Cajal's frozen-section method "à l'hydroquinone" has been employed for nerve fibres and nerve endings, whilst Cajal's gold-sublimate method and, more extensively, several variants of Hortega's method have been used for neuroglia. Hortega's method has also been used for the demonstration of connective tissue, blood-vessels, &c. Complete details of the various staining procedures are given in English by Addison and Penfield in the chapters which are devoted to neurological technique in McClung's "Handbook of Microscopical Technique" (1929 edition).

Structural Elements of the Neurohypophysis.

Blood-vessels with their accompanying connective tissues, neuroglial cells with their processes, and bundles of nerve fibres are the structural elements which together form what may be considered the fundamental texture of the neurohypophysis and must be discussed in relation to the nerve endings to be found in the organ. Migratory elements such as pigmentary cells, epithelial cells derived from the pars intermedia, and the recently described (Vazquez-Lopez, 1942) microglial cells of the region occur in large numbers but demand no further mention in the present connection. To facilitate description, attention will at first be given almost exclusively to the pars nervosa (infundibular process).

Connective Tissue and Blood-Vessels.

In the pars nervosa three fibrillar systems are found intermingled—connective tissue fibres, nerve fibres and fibre-like prolongations of neuroglial cells. To avoid errors in the identification of these different elements requires detailed familiarity with the morphology of the structures themselves and accurate knowledge of their characteristic distribution. Silver and gold impregnation methods are used on account of their high specificity but results are apt to be erratic. Technical difficulties are, however, not insuperable. It has to be realized that the specificity of these impregnation methods, though high, is only relative, not absolute. It can be stated, however, that by the skilful use of this or that recognized modification of the fundamental technical procedures it is possible to produce with fair certainty sections which show any one of the three fibrillar systems to the almost total exclusion of the other two. It is even possible to show something of all three fibrillar systems in the one section, though less clearly. Whenever conditions have been such as to pick out considerable lengths of fibre, indentification presents little difficulty. But when for some reason only isolated short lengths of fibril have taken the stain, even

with high specificity, identification becomes difficult since the stained bits of fibril are apt to be too short to present distinguishing characters. In extreme cases the lengths of stained fibril may be so short as to make it quite impossible to say whether they are bits of nerve fibres, bits of connective tissue reticulum, or bits of neuroglial fibrils. More than one published report of studies of neurohypophyseal histology contain within themselves evidence of failure to secure sections sufficiently well stained to give confidence in the conclusions drawn by the author. It must be emphasized again that for the identification of each fibrillar system recognition of the morphological characters of its fibres and of the way in which these fibres are disposed in the tissue is of more importance than any supposed specificity of some particular staining method. To minimize risk of error in identification is one reason for careful study of the connective tissue in the pars nervosa.

Connective tissue in the pars nervosa has much the same appearance and function as connective tissue elsewhere. At the surface of the organ it forms a sort of capsule and within the substance of the organ it accompanies the blood-vessels and helps to form a supporting framework. The amount of fibrous tissue varies greatly from species to species. Where it is minimal, as in the horse, it is relatively simple in arrangement, the arrangement of the other structural elements of the organ is also relatively simple, and histological demonstration of the several structures is correspondingly easy.

In the horse the pars nervosa is almost completely enveloped by the pars intermedia and throughout most of the area of this contact the connective tissue capsule of the pars nervosa is poorly developed, is everywhere thin and loose in texture, and in many places is not present. The collagenous and reticular fibres never attain more than moderate thickness. They are never densely aggregated and they separate the parenchyme of the pars nervosa so incompletely from that of the pars intermedia that contact and communication between the two parts must be regarded as practically uninterrupted. Towards the extreme distal end of the pars nervosa the capsule thickens and becomes more compact in texture, its reticular fibres becoming more regularly arranged and lying parallel to the surface of the organ. Maximum thickness is reached at the tip of the pars nervosa where at one or more points the enveloping pars intermedia disappears and permits establishment of continuity with the fibrous dural tissue which lines the base of the skull. This is the region where in the embryo, before the meninges become differentiated, the distal pole of the neurohypophysis is fixed to the mesenchyme of the base of the skull. It constitutes a sort of hilum through which the inferior hypophyseal arteries enter the organ. The reticular fibres of this thickened cap-like portion of the capsule cover and protect nerve fibres of special corpuscles which under the name of "meningeal terminal corpuscles" will be described later in the present paper.

Within the substance of the pars nervosa of the horse, connective tissue is confined to a definite but thin coat of delicate fibres which closely and completely envelops the vessels of medium calibre and, less completely, even the smaller vessels and capillaries. Sometimes this fibrillar tunic is the only visible evidence of the vascular net which extends throughout the distal part of the organ. Connective tissue of the tunic never extends beyond the immediate proximity of the vessels and its outer limit is rather sharply defined.

Immediately outside the connective-tissue tunic is what may be called a peri-vascular space since in ordinary histological preparations it has a hyaline appearance and is relatively devoid of formed elements. The perivascular space surrounds even the small vessels. It is not always of the same relative diameter—the diameter is often three to four times that of the lumen of the vessel—but it is always detectable (fig. 1). It is

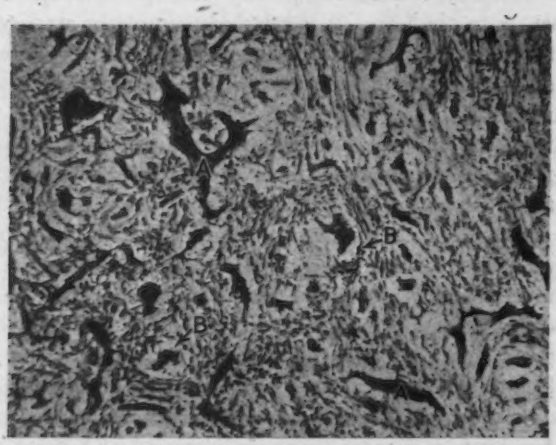

FIG. 1.—Perivascular spaces in the pars nervosa of the horse hypophysis. Low magnification. Hortega's silver carbonate stain. Many vessels (A) are seen. Round each there is a clear zone, the perivascular space (B) which is almost free of cells. The numerous small elements (C) are neuroglial cells.

particularly evident around the vessels near the pars intermedia. The outer limits of the perivascular spaces are generally sharply revealed by the bundles of nerve fibres which crowd the proper substance of the organ right up to the outer limits of the spaces. When the blood-vessels of the pars nervosa are seen in transverse section the presence of the perivascular spaces gives that peculiar appearance which led Herring (1908) to describe

the tissue elements as being "arranged in whorls around the vessels." The perivascular space has been noticed also by later writers—Costa (1923), Collin (1924), Roussy and Mosinger (1933*a*, 1937) and others—and interpreted as being due to the presence of secretion substances, either deposited or in course of transit. Whatever its function, this perivascular space, of variable thickness, devoid of connective tissue fibres and almost totally free of cellular elements, is an obvious and striking characteristic of the neurohypophysis of the horse (fig. 2). It will be mentioned again later.

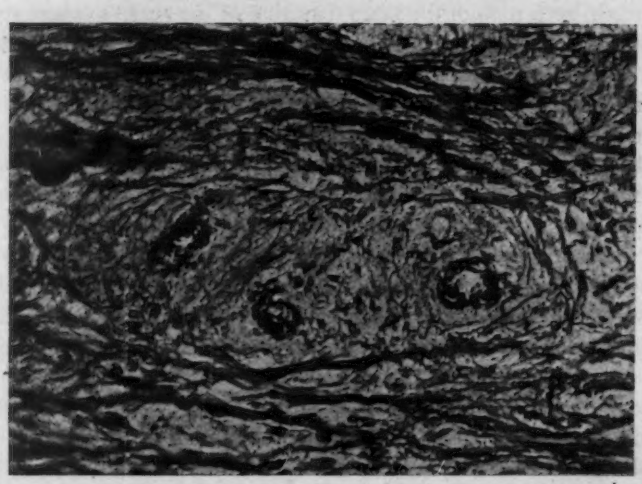

FIG. 2.—Perivascular spaces in the pars nervosa. High magnification. Cajal's silver nitrate stain. A single perivascular space occupies most of the central area of the picture. Only the slender terminal nerve fibrils enter this zone, the crowded nerve bundles of the region pass it by. The associated vessel is seen within the space, cut at three separate points of its very tortuous course.

In the horse numerous blood-vessels pass through the capsule of the pars nervosa and the vascular connections between the pars nervosa and the pars intermedia are particularly rich. The main blood-vessels are of medium calibre and are much alike in diameter. They are very numerous. In the neighbourhood of the stalk most of them run parallel to the long axis of the organ, whilst in the distal part of the organ most of them run transversely, forming a sort of criss-cross or lattice of wide mesh. Intermingled with this arborization of larger vessels many of more slender appearance are found. Special methods for the study of blood-vessels have not been used in the present studies, but so far as can be determined

from silver-impregnated preparations in which it is often necessary to rely upon observations of the enveloping connective-tissue sheath rather than upon recognition of the vessels themselves, branching of the larger vessels of the pars nervosa is relatively infrequent. Even in the more distal portion of the organ, where vessels are to be seen cut at all angles, the appearances are deceptive, for they are due to the tortuous course of the main vessels rather than to numerous diverging branches. In thin sections of the organ one and the same vessel may be cut repeatedly in quite a short length, even though the main direction of the vessel's course remains fairly straight. This zig-zag course, giving at times the appearance of a kind of glomerulus, can often be followed for some distance in thick frozen sections. Some authors have already observed similar appearances in other parts of the neurohypophysis.

In the pars nervosa of some species there is more connective tissue than in the horse. The vascular tunic is, for instance, more fully developed in the rabbit. In this animal the loosely arranged connective tissue fibrils extend into and pervade the whole of the perivascular space, everywhere reaching to its outer limits but nowhere extending further than this into the proper substance of the organ. Indeed, so strict is this coincidence in extent in the rabbit that it is during studies of the connective tissue in this animal that one becomes most fully conscious of the reality and continuity of the perivascular space and the way in which it forms an arborizing structural entity extending throughout the organ.

In the pars nervosa of some other species the connective tissue is still more highly developed. In the ox, for example, the capsule is thick, and dense reticular tissue extends throughout the whole parenchyma of the organ. Everywhere connective tissue passes in from the capsule and joins up with that of the vascular tunics. Particularly prominent are the masses, almost fibrous in character, which arise from the area where the capsule is more or less completely fused with the diaphragm of dura which separates pituitary gland from the base of the brain, and then spread out within the substance of the organ. In the ox the ubiquitous character of the connective tissue obscures the fundamental morphological plan of the organ; the several parts have become more irregularly disposed and more difficult to demonstrate.

Nerve Fibres.

The presence of bundles of nerve fibres in the pituitary stalk and pars nervosa was first described by Cajal (1894) in rats and mice. His

findings were soon confirmed by, among others, Gentes (1903), Gemelli (1906) and Tello (1910), the latter using human material. The fibres were also studied by Nicolesco and Railneau (1925), Pines (1925), Greving (1926), Stengel (1926) and Roussy and Mosinger (1933*a*, 1933*b*), all of whom were principally interested in tracing their origins. Cross (1928) described nerve fibres in the rabbit's pars nervosa. More recently Bucy (1930, 1932) has studied these fibres in the ox, and Hair (1938) has studied them in the cat. Rasmussen (1938) confirmed their presence in extraordinary numbers in man and attempted quantitative estimations. But many observers, even of recent date, deny that any considerable number of nerve fibres is present in the neurohypophysis. Disputation has mainly involved the problem of identification, for that stainable fibres do exist in large numbers in the neurohypophysis is generally admitted. Some published illustrations and descriptions show that what their authors studied were really nerve fibres although at the time they were considered to be of different nature. Koelliker (1896) even pointed out the extraordinary length of these fibres and noticed their varicosities, features which must now be regarded as diagnostic of nerve fibres, and yet he thought the fibres were neuroglial. Herring (1908) also mistook the real nature of the fibres although he could impregnate them by the Cajal nitrate method which had been specially devised for the specific staining of nerve fibres. Hoenig (1922) used a similar technique and reached similarly mistaken conclusions. Balado (1939) whose photomicrograph No. 4B shows what must now be regarded as indisputable bundles of nerve fibres, failed to recognize them as such, probably through an unfortunate reliance on the absolute specificity of Holzer's neuroglial stain. The nerve fibres indeed have usually been regarded as neuroglial when their true nature has not been recognized. Mistakes seem to have arisen most often from too great or too little reliance upon the specificity of some method of staining. In the neurohypophysis, an organ which under natural conditions is rich in peculiar substances of debated physico-chemical nature, stains are apt to show reduced specificity. Thus Popjak (1940) has claimed that by Holzer's method, which is usually considered specific for neuroglia, it is possible to stain the neurohypophyseal colloid all along the course of the hypophyseal-hypothalamic nerve tracts and even inside the hypothalamic neurones. There is also the fact that nerve fibres of the stalk and the pars nervosa, perhaps on account of their extraordinarily dense concentration in this region, may sometimes stain partially or completely by methods which when used in other parts of the central nervous system do not show the

least affinity for nerve fibres. Correct identification rests much more securely on the recognition of morphological characteristics of the nerve fibre, its course and its ultimate termination. For example, nowhere in the central nervous system is it possible to find neuroglial fibres of the length of these debated fibres of the neurohypophysis.

The nerve fibres destined for the neurohypophysis arise in the various hypothalamic nuclei. At first, at least in the horse, they pursue a sinuous course through the eminentia media of the tuber cinereum where they form the greater part of the tissue substance. As they approach and enter the stalk the fibres are found gathered together in thick, close-set, readily stainable bundles which occupy the large medial or central portion leaving a narrower peripheral zone, in contact with the pars tuberalis, which is usually described as nearly or completely free of nerve elements. In reality this peripheral zone contains an abundance of thin fibres which are both differently and less regularly disposed than those of the central area. The fibres of this peripheral zone will be referred to again when the nerve endings of the region are under discussion. The stalk itself consists essentially of the densely aggregated nerve bundles which here run, like the main blood-vessels, in a straight path and in a longitudinal direction. In the lower portion of the stalk the compact formation of the nerve bundles begins to be broken up by the passage of transversely disposed blood-vessels and then, as the nerve bundles enter the pars nervosa, they begin to spread fan-wise (Plate I, fig. 4). Through the upper part of the pars nervosa the bundles run an almost straight course, becoming progressively thinner. In the distal third or so of the organ the course of the attenuated bundles is much less regular and, like the blood-vessels of this same region they are found running in all directions, specially transversely (Plate I, fig. 5). In fact, in this distal part of the pars nervosa there is an almost felt-like arrangement of nerve fibres and blood-vessels. But, as already mentioned, vessels and nerve bundles do not come into actual contact. Around the vessels there is always the perivascular space, the zone which is never invaded by the bundles of nerve fibres which pass along following its contour and crowding the tissue substance (fig. 2).

Mention must be made of a system of nerve bundles which lies beneath the connective tissue capsule of the pars nervosa in its more distal part. Here, as the capsule becomes thicker and passes beyond the limits of the enveloping pars intermedia to reach the apex of the pars nervosa, the nerve bundles become steadily larger. They end in the special meningeal terminal corpuscles which lie embedded in the thick fibrous covering of

the apical region. At the base of each corpuscle bundles of nerve fibres emerge from the body of the organ, forming a pedicle of great relative thickness, and then expanding bouquet-like in the body of the corpuscle (fig. 3). Many fibres become myelinated as they approach and enter the corpuscle; in all other parts of the neurohypophysis nerve fibres are non-myelinated. In the neighbourhood of each corpuscle and also within its substance much connective tissue, chiefly in the form of reticular fibrils, is found amongst the nerve fibres and in these situations it constitutes much of the tissue mass (Plate VII, fig. 18). The corpuscles, which are

FIG. 3.—Meningeal terminal corpuscle. Low magnification. Cajal's silver nitrate stain. The multitudes of nerve fibres, which are the main structural element, are well seen. A, pars nervosa; B, pars intermedia; C, dura mater lining base of skull; D, large blood-vessels.

never more than two or three in number, lie amongst and are closely surrounded by the numerous blood-vessels which enter the pars nervosa at its distal pole.

NEUROGLIAL CELLS.

Retzius (1894) carefully studied the neuroglial cells of the neurohypophysis and identified them as such. Later came Berkley (1894), Herring (1908), Tello (1910), Hoenig (1922), Pines (1925), Ibañez (1935)

and others who studied these same cells in various species of animals and with various methods of staining. Most of them accepted the cells as neuroglial. But the most important report on the structure and nature of these cells is that of Bucy (1930), who studied ox pituitary and used modern methods of silver impregnation. His choice of the ox was perhaps unfortunate, for in this animal the neuroglial cells of the hypophysis are of rather extreme form. Because of the significance he attributed to certain morphological characters which he observed in these cells, and because the cells failed to take certain stains which he regarded as specific tests for neuroglia, Bucy concluded that the neuroglial cells of the hypophysis are not the same cells as the classical neuroglia found in the rest of the central nervous system. To emphasize what he considered to be fundamental differences and to avoid confusion he called the hypophyseal neuroglial cells "pituicytes." More recently Griffiths (1938, 1939, 1940) supported Bucy's view, though he did point out the close relationship which subsists between pituicytes and the common astrocytes. Weaver and Bucy (1940) have used the local presence of the pituicyte and the corresponding absence of the classical neuroglial cells as one reason for considering the eminentia media as anatomically distinct from the rest of the tuber cinereum. This insistence on the special character and individuality of the pituicyte has had far-reaching influence upon physiological thought, especially in America, for the presence of a special kind of cell has made it easy to attribute glandular function to the neural lobe with these cells as the special functional units. Gersh (1937, 1939) has described morphological criteria of secretion in the cells of the neural lobe of rats under experimentally produced conditions of restricted diuresis, and these cells, which have long been known, he has named "parenchymatous glandular cells." Recently Hare, Hickey and Hare (1941) have repeated the experiments of Gersh, but they have been unable to find any correlation between the hormonal antidiuretic content of the pars nervosa and the osmiophilic droplets of the "parenchymatous glandular cells" in rats deprived of water for various periods or in rats with permanent polyuria after section of the pituitary stalk. Our observations in rat's pituitary are also in disagreement with Gersh's view, but a detailed report of these studies is outside the scope of the present paper. The bearing which morphological appearances may have on the general question of secretion by hypophyseal neuroglia will be the subject of a forthcoming paper.

The neuroglia of the neurohypophysis can be demonstrated by the

methods commonly used for staining neuroglia in other parts of the central nervous system. Cajal's gold-sublimate method does not, as a rule, succeed well in the pars nervosa of the horse, but in the corresponding organ of the rabbit the pituicytes are regularly stained with delicacy and specificity. Rio-Hortega's silver carbonate method in its several variations gives consistently good results in the various species of animals so far examined. Penfield's modification with hydrobromic acid is especially valuable when it is desired to study the arrangement of neuroglial cells within the organ. The method is one by which these cells are impregnated with great selectivity although not, as a rule, with the delicacy seen when the Hortega method is used.

In the stalk and in the upper part of the pars nervosa the arrangement of the neuroglia is at its simplest—is almost schematic in fact—owing to the exceptional regularity in the arrangement of nerve bundles and blood-vessels of these parts. In other animals and even in other parts of the neurohypophysis of the horse the inter-relationships of our three tissue-elements are more difficult to follow. At first therefore attention will be centred upon conditions found in the less complex regions of the horse hypophysis (Plate II, fig. 6).

Here in the horse, then, the neuroglial cells, lying as they do amongst the close-packed, longitudinally-arranged nerve fibres and blood-vessels, give the impression of being arranged in longitudinal columns or strings. Under high powers the neuroglial cell is found to consist of a large, ovoid, finely granular nucleus surrounded by a rather scant, irregularly shaped cell body which itself is irregularly extended in a large number of long protoplasmic processes. The processes are shorter than those of the corresponding cells of the ox, but even so they spread so widely in three-dimensional space and there is so much overlapping of cell limits that only rarely is it possible to trace the whole extent of an individual cell. In spite of this handicap it is soon clear that the neuroglia has a definite orientation in relation to both nerve bundles and blood-vessels. Closer study shows that the bodies of the neuroglial cells lie closely applied to surfaces of the nerve bundles. They lie mainly, in fact, upon those surfaces which nerve bundles present to the perivascular spaces and thus, as a single layer, the cell bodies form a diffuse and very incomplete sheet or net stretching round the perimeter of the perivascular spaces. The thin flattened cell bodies are often elongated and cells stretching in all directions are met with, for the direction of elongation bears no constant relationship to the course of either nerve fibres or blood-vessels. In one

direction the neuroglial cells send short processes in amongst the adjacent nerve fibres which form the bundles and in the other they send numerous longer processes stretching across the perivascular space to end in vascular feet in the wall of the blood-vessel (Plate II, fig. 7).

In the distal parts of the pars nervosa relationships are still more difficult to observe since nerve bundles and blood-vessels here run in all directions indiscriminately. Presumably the architectural plan is essentially the same as in the more proximal parts of the organ. Everywhere processes of neuroglial cells can be clearly seen stretching across the perivascular spaces to end in relation with the vessels, whilst nuclei and bodies of neuroglial cells are found mainly in the areas where the nerve bundles are—seldom, if ever, in perivascular spaces.

Sites of Nerve Endings.

The course and anatomical relationships of the nerve bundles of the neurohypophysis of the horse have been described in preceding paragraphs. Most of the constituent fibres end in one or other of the following sites: (*a*) the perivascular spaces; (*b*) neighbouring parts of the pituitary body; (*c*) the terminal meningeal corpuscles.

Nerve Endings in the Perivascular Spaces.

The relatively simple anatomical arrangement of structural elements which makes the upper portion of the pars nervosa the most suitable area for the preliminary investigation of the neuroglia also makes the region especially favourable for observation of the terminal portions of the nerve fibres which end in relation to blood-vessels. Throughout the eminentia media and the stalk, the nerve fibres are found gathered closely into thick bundles in which they run parallel and comparatively straight courses. At all points along these bundles individual fibres are seen emerging at sharp angles to enter the immediately adjacent perivascular spaces. These issuing fibres are readily recognized by this characteristic feature that they run in a direction transverse to that of the fibres of the bundles; they are also thinner. In the pars nervosa the course of nerve bundles is much more irregular and less easily followed and in practice it is correspondingly difficult to use sharp change of direction as a criterion in the identification of terminal fibres.

In the perivascular spaces these terminal portions of the nerve fibres assume completely new morphological characters. They begin to twist and turn and they become contorted and of uneven thickness. They

become in fact exactly like the terminal fibres which constitute and characterize all ending-apparatus in other parts of the body. Sometimes they take several successive short spiral turns round the vessel; sometimes they lie along the vessel making a short series of lateral sweeps of high amplitude, but short period; sometimes they resemble a tangled skein lying in the perivascular space and often, whilst following a general course more or less parallel to that of the blood-vessel, they make a succession of rapid sweeps right from the inner to the outer limits of the space (Plate III, fig. 8). In fact there can be few possible contortion figures which are not sometimes found. A terminal nerve fibre will often exhibit several contortion forms in succession. In the zig-zagging part of their course terminal fibres generally give off a number of short collateral branches each of which ends in a small terminal mass, "bouton" or ring. These terminal enlargements occur in large numbers in all parts of the perivascular spaces. They show no particular tendency to aggregate on the vessel wall.

Some terminal masses and swellings are distinctly larger than those just mentioned. They occur most often in groups or bunches, generally at the ends of terminal arborizations of nerve fibres (Plate IV, fig. 10), perhaps also in groups at the ends of collateral branches. Similar swellings occur along the course of the winding tortuous nerve filaments of the perivascular space and they often occur at points where collateral branches arise. The nerve fibre itself is often thickened for short lengths of its course, particularly at places where the course is undergoing frequent and sharp changes of direction, but these thickenings are perhaps only more primitive forms of the swellings. Swellings; including the terminal masses, take many forms—bulbs, clubs, spatulæ, menisci, &c.—and sometimes the fibre protrudes from the distal end of what otherwise would be regarded as a terminal mass. These swellings and masses, which Tello (1910) seems to have observed in human pituitary body and regarded as regeneration bulbs, are exceptionally large and numerous in the pituitary body of the horse. In this animal it is difficult to find any area of the neurohypophysis where they are not present in large numbers (Plate III, fig. 9; Plate IV, fig. 11).

Very often giant expansions are seen. These may reach a length of 100 microns or more; often they occur in clusters and they are usually terminal. They are of various shapes and are probably generally thin flattened expansions rather than bulbous masses. It is possible that when a single one is seen in a histological section it is just one of a group or

cluster, the others having been cut away when the section was made. Giant expansions are usually impregnated homogeneously, but sometimes they are seen to have a finely reticular structure—a neuroreticulum—similar to that of the bulbs and menisci of lesser size. Generally these giant expansions occur at the end of a fibre which has shown a considerable degree of thickening in its course. Sometimes they are so large that it seems difficult to believe that they are entirely contained within the limits of the perivascular spaces—unless indeed the space is specially enlarged to accommodate them. Sometimes they seem to have definitely extended into the nerve bundles and the same may be said of some few bulbs of smaller size. From the frequency with which these giant expansions occur entirely within the perivascular spaces and from their close resemblance to the swellings and masses more usually seen on terminal fibres of the perivascular spaces it is assumed that giant expansions are probably only special forms of these (Plate VI, fig. 14).

The terminal fibres winding and coiling in complicated pattern in the perivascular spaces overlap and form an open texture filling those spaces more or less completely and evenly throughout their whole length and breadth. They do not form a real plexus; no fusion of fibres can be found and the conclusion is drawn that each fibre remains distinct throughout its course. Presumably each succeeding length of perivascular space is supplied with fibrils which leave the neighbouring bundles in more or less orderly succession. Often an incoming fibre is seen to run along the perivascular space for a short distance before becoming twisted and convoluted in the manner typical of terminal fibres proper. During this short course the straightness of the path which the fibre follows is in sharp contrast with the complicated windings of the other fibres among which it passes. In the stalk terminal fibres are particularly numerous and form a pattern of correspondingly close texture in the perivascular spaces. Here the entering fibres all take at first a straight longitudinal course at the periphery of the space where together they form a distinct tract running parallel to the blood-vessel; they form a layer lying between the nerve bundles and the convoluting terminal fibres which occupy the remaining more central part of the perivascular space. The fibres of this peripheral or marginal tract of the perivascular spaces of the stalk are very slender and although they often run beside and parallel to the fibres of the main bundles they are easily distinguishable by this difference in thickness. That fibres are continually entering the peripheral tract is clear and it is equally clear too that fibres are continually leaving the tract to become convoluted

terminal fibres, but generally it is impossible, as before stated, to trace any individual fibre throughout its length. In the pars nervosa there are fewer terminal fibres in each perivascular space, the pattern of fibres is of more open texture, and individual fibres can be followed for much greater distances than in the stalk. In the pars nervosa, entering fibres do not take a preliminary longitudinal course through the peripheral zone of the space: they go more directly to their destination. They can be seen entering, sometimes singly, often in groups, and assuming straightway the convoluted character of terminal fibres.

Earlier in the present paper passing mention was made of the somewhat narrow zone of tissue, supposedly free of nerve fibres, which forms the outer or cortical part of the eminentia media and stalk where these adjoin the pars tuberalis (Plate VI, fig. 16). In reality this zone is very rich in nerve fibres and nerve endings; they are associated with blood-vessels of the region. There are no bundles of trunk fibres in passage to other areas, near or distant, but otherwise conditions in this outer zone are much as in the larger, more central region of the stalk which has just been described. There is the same wealth of nerve-ending apparatus in the perivascular spaces and there is the same tract or sheet formed just within the periphery of those spaces by the very numerous delicate terminal portions of the fibres on their way to points where turning more deeply into the spaces they will assume the character of nerve-ending apparatus. These thin fibres which are thus gathered together in the marginal zones of the perivascular spaces run like the blood-vessels with which they are associated in a transverse direction. In histological preparations these fibres give a characteristic appearance to the tissue, for in the absence, already noted, of neighbouring bundles of thick fibres, there is nothing to confuse the picture. The slender fibres are, however, difficult to stain (Plate VI, fig. 16).

Thus throughout the neurohypophysis the typical nerve-ending apparatus is found in a profusion such as is rarely equalled elsewhere in the body. Within the organ, regional differences of minor importance are found in such characters as richness of the innervation, pattern of the windings and convolutions or in the number and predominant shapes and sizes of the swellings and terminal masses, but taken as a whole the appearance is that of one co-ordinated system devoted to some special function.

Fibres Ending in Neighbouring Parts of the Gland.

Although most workers who have studied the innervation of the pituitary gland are agreed that nerve fibres do pass from the pars nervosa

to the pars intermedia there is no general agreement as to the number of fibres involved or even as to the points at which the fibres cross the boundary. Most of the discrepancies between published descriptions have arisen, in all probability, because available staining methods are erratic in action and because these methods have never been found staining the whole of the nerve fibres at any one time. Observations made in the course of the present investigations warrant certain statements in amplification, support or correction of current views.

In the horse the area of contact between the pars intermedia and the pars nervosa is unusually extensive and the common boundary, as seen in histological sections, has a very irregular contour. Numerous masses of epithelial tissue jut into the substance of the pars nervosa or form islets more or less deeply embedded in that tissue. The separating layer of connective tissue is nowhere thick and at many points is practically absent. Everywhere large numbers of nerve fibres cross the boundary to enter the pars intermedia. They cross in special abundance from that area of the neurohypophysis where stalk merges into pars nervosa (Plate V, fig. 12). Most of the blood-vessels which cross the boundary are accompanied by considerable numbers of nerve fibres, but there are also many fibres which, alone or in bundles, cross at other points.

Nerve fibres enter the pars intermedia at all angles, or, to state the same fact in another way, the highly irregular contour of the boundary cuts across entering fibres at all angles. Most fibres never again return to the pars nervosa. A few behave differently. Fibres running a more or less straight course along the pars nervosa may pass right through an invading mass or a detached islet of epithelial tissue and continue on their course. Such fibres often supply collateral branches to the epithelial tissue as they pass through (Plate V, fig. 13).

Those nerve fibres which cross into the pars intermedia unassociated with blood-vessels pursue a very irregular course, turning this way and that to gain passage between the large, closely packed cells of the epithelial cords. Soon they take on some of the characters of nerve-ending apparatus. Expansions—bulbs, menisci, &c.—appear in the course of the fibres just as we have seen in the pars nervosa, but they are usually smaller than in that organ. Terminal expansions are comparatively rare amongst the epithelial cells of the pars intermedia; most often the fibre is seen to emerge again at the distal end of the expansion and continue on its course. Frequently the swellings occur at points of ramification, but not more than two or perhaps three collaterals have been seen issuing from any one

of them. Sometimes no swellings are present at all and then the terminal fibre appears simply as a wavy contorted filament. The nerve fibres seem to run in immediate contact with the epithelial cells. Similar terminal fibres are frequently seen in the connective tissue septa of the region.

It is not clear how, if at all, these fibres and endings of the system of nerves entering from the pars nervosa are related to the less gross pericellular plexuses and nerve-ending apparatus which various authors report having found intimately associated with and closely surrounding the epithelial cells of the pars intermedia. Information obtainable from the preparations used in the present investigation is inadequate. It seems worthy of remark, however, that although, in our preparations, the nerve fibres in the pars nervosa as well as those which pass thence into and through the substance of the pars intermedia may often be seen sharply, satisfactorily, and apparently totally impregnated, we have only occasionally, and never completely, succeeded in demonstrating pericellular plexuses. In connection with this system of nerve fibres derived from the pars nervosa it is consistently possible to demonstrate collaterals which end between the epithelial cells in small varicosities or rings, but it has proved beyond our powers to trace with certainty a definite continuity between these nerves and the pericellular plexuses of the epithelium. It is obvious that the epithelium of the pars intermedia is richly innervated. It is obvious also that efforts towards an understanding of this innervation are handicapped by gaps in our knowledge.

A certain number of the nerve fibres which enter the pars intermedia from the pars nervosa seem to find their way right across that organ and enter the pars anterior (distalis). Such passage is readily possible at many places in the horse because in the horse the cleft is very small and anterior and posterior lobes are in organic contact over a considerable area. The actual number of fibres seen crossing into the pars anterior is comparatively small in our preparations, but numbers seen may not be an accurate indication of total numerical importance since in our hands impregnation of nerve fibres becomes less and less satisfactory as distance from the pars nervosa increases.

It would appear that many of the nerve fibres which enter the pars intermedia in company with the blood-vessels maintain that relationship throughout. They are found in the vascular adventitia, especially in the adventitia of vessels of medium calibre. Some of the nerve fibres which accompany a vessel presently form bunches of thinner collaterals which straightway end beside the vessel in menisci or bulbs of typical arrange-

ment and of neuroreticular structure. Sometimes such arborizations are clearly terminal (Plate VI, fig. 15). At other times expansions occur in the course of a nerve fibre. Beyond the expansion the nerve fibre may either continue its course beside the vessel to end ultimately in the perivascular area like those fibrils just described, or it may turn into the neighbouring epithelial cords, there to assume all those characters which are found in the nerve fibres derived more directly from the pars nervosa. A close relationship seems therefore to exist between the nerve endings found in relation with the vessels and those found in relation to the epithelium in spite of the fact that the difference in terminal sites might at first suggest differences in function.

Nerve Endings of the Meningeal Terminal Corpuscles.

The broader features of the meningeal corpuscle have been described already (fig. 3; Plate VII, figs. 17 and 18). We have seen that for the most part its substance consists of multitudes of nerve fibres which run in a roughly longitudinal direction and lie intimately mingled with numerous similarly disposed connective-tissue fibres. We have seen also how this somewhat compact and characteristic corpuscular tissue first takes shape within the substance of the pars nervosa in what may be regarded as the base of the corpuscle and extends thence through a short wide peduncle to form the expanded corpuscle-head which lies embedded in the meningeal fibrous tissue. Mention must now be made of the nerve endings which abound in the terminal corpuscles.

We have seen already that the nerve fibres destined for meningeal corpuscles are found in the distal part of the pars nervosa gathering together in the form of a sheet which lies just beneath the capsule and becomes steadily thicker and more prominent as the apex of the organ—the site of the corpuscles—is approached (Plate VII, fig. 18). Constituent fibres of this sheet-like system join at all points. They are derived from bundles which during their passage through the pars nervosa have supplied the perivascular spaces. Many are derived from bundles which run near the periphery of the organ and have never been completely dispersed, but those fibres which come in from the more central area of the organ arrive mainly as isolated fibres, for the bundles of which they once formed part have been thoroughly broken up in passing through the rich and very complex vascular network of the region.

The head of the corpuscle is lobulated as a rule, each lobule receiving its own mass of nerve fibres. In some horses there is only one meningeal

terminal corpuscle. In others there are two or even three and then all arise in the same small area and all are smaller in size. Sometimes a group of fibres may leave a corpuscle, run for a short distance in the meningeal connective tissue, and end in a tiny detached corpuscular mass. Occasionally isolated fibres or even small bundles belonging to the corpuscular system run for longer distances in the dural substance.

All parts of the meningeal terminal corpuscle—base, peduncle and head—are characterized by the presence of a very remarkable number of nerve-ending apparatus. Everywhere, in association with the nerve bundles, there are swellings and masses of medium size similar to those already described as seen in the substance of the pars nervosa. Their numbers are the chief feature of the tissue pattern seen in histological preparations. They vary a little in both size and shape, but the general tendency is towards rounded forms—ovoid, spherical or pear shaped. They have a very fine neuroreticular structure. They form true and obvious bunches everywhere, and these are specially noticeable in those parts of the corpuscular base which lie close to the pars intermedia. Often indeed proximity to the pars intermedia is so intimate that these nerve-ending masses may be seen lying in between epithelial cells. Swellings and masses (Plate VIII, fig. 19) are less abundant in the peduncle, but in the head of the corpuscle almost every fibre seems to end in globoid masses which are all of large size and all much alike (Plate VIII, fig. 20). These large masses are taken to be the essential functional elements of the meningeal terminal corpuscle.

Within the corpuscle the nerve fibres are thick and closely arranged and, as already noted, some of them are myelinated almost to their globoid endings. The whole texture in fact strongly resembles that of ordinary nerve cords. Lying in amongst the nerve fibres and connective tissue fibrils there are many cell nuclei arranged in parallel rows in conformity with the direction of the fibres and fibrils (Plate VII, fig. 17). No attempt has been made to identify the cells to which these nuclei belong. The position of the large bulbous nerve endings can be observed even when simple stains have been used, for though unstained these formations are large enough to appear as empty spaces of appreciable size (Plate VII, fig. 17).

The meningeal terminal corpuscles of the horse seem to be unusually well developed. They are visible to the naked eye and may reach one or even two millimetres in diameter. In the rabbit the same essential corpuscular elements can be recognized, but they are more diffusely arranged.

Isolated nerve fibres are seen penetrating the apical region of the fibrous capsule, there to end immediately in globoid expansions which are exactly like those found in the head of the meningeal corpuscle of the horse.

Bucy (1932) and Rasmussen (1938) have described nerve fibres in the connective-tissue capsule of the pituitary body and ordinary sensory corpuscles have been described by Collin (1933) in areas of the meninges near to the pituitary body, but the special corpuscular nerve endings seem not to have been noticed hitherto.

Significance of the Nerve Endings.

Much has been published concerning each of the various structural elements of the neurohypophysis save only the nerve endings. Of these and of their arrangement in the organ little is known. There are vague references to nerve endings around the neuroglial cells (Bucy, 1930, 1932) or around the blood-vessels (Croll, 1928), but most workers who have studied hypophyseal innervation either make no mention at all of the actual nerve endings or else state explicitly that it is impossible to follow nerve fibres once they leave the bundles which, coming from the stalk, spread out in the substance of the pars nervosa. Brooks and Gersh (1941) have stated recently that in the rabbit "no clear nerve endings were observed in the infundibular process" and that in the rat they occasionally observed the "parenchymatous glandular cells" which are peculiar to this animal, enveloped by a reticulum formed by small collateral branches of the nerve fibres. A critical appraisal of the work is difficult since the authors give no illustrations and their paper contains few details, but they seem not to have added much to Cajal's (1894) original description.

Tello (1910), who studied human material, is the only author who makes clear and specific references to terminal formations in relation to neurohypophyseal nerves. He describes the nerve fibres in the vascular adventitia of the stalk and pars nervosa and draws attention to this relationship to blood-vessels. Without being able to demonstrate the actual terminations, he concludes that most probably "the fibres exhaust themselves by dint of turning round the vessels." He described small club-shaped and ring-shaped endings and clearly pointed out how dense is the ramification of nerve fibrils around the blood-vessels of the stalk in comparison with that around the vessels of the pars nervosa. In the present study a similar difference has been found between the same two regions in the horse, as already mentioned. Tello was the first to describe bulbs and menisci at the ends of considerable numbers of neurohypophyseal

fibres, but he was using human post-mortem material and supposed that those structures must be the result of previous pathological processes. This error of interpretation is understandable, for the period was one in which the functional importance of the pituitary body was regarded as negligible. He interpreted the bulbs and menisci as morbid structures, for what useful function could explain their observed abundance in a supposedly semi-atrophic organ? He found them in persons of all ages and thought them most easily explained as the result of degenerative and regenerative processes occurring at the ends of nerves which had sustained damage as a result of the migration of cells of the pars intermedia. His careful description of the various forms and other characters of these supposedly degenerative and regenerative structures show that the structures he saw in man were similar to the swellings and masses which we have seen in the horse in the same profusion in similar situations. Their existence—especially the existence of bulbs and clubs—has recently been confirmed in the ox by Bucy (1930), in the cat by Hair (1938) and in man by Rasmussen (1938). But though opinions as to the function and importance of the pituitary gland have changed considerably with the passage of time the interpretation offered by those more recent workers does not differ from that given by Tello in 1910. Rasmussen (1938) considers the structures to be "incidental structures if neural at all" and in agreement with Bucy he relates them to the much discussed Herring bodies. Thus of all conceptions of neurohypophyseal structural elements this explanation of the terminal bulbs is one of the very few that have remained unchanged for the past twenty-five years.

The fundamental plan upon which the pars nervosa is built up has been described in previous pages. With the knowledge thus provided it is fairly easy to establish with certainty the anatomical relationships of the nerve endings. From what has been said it is clear that the terminal fibres and their end-apparatus are exclusively situated along the course of the blood-vessels. They are distributed throughout the whole extent of the space, the perivascular space, which everywhere surrounds the blood-vessels. This close anatomical relationship with the vessels on their course through the organ is obviously significant.

As Rasmussen points out in discussing human tissue, it is clearly impossible to deny that the nerve fibres may come into physical contact with the neuroglial cells or their processes. But the very fact that such contacts would be with the neuroglial processes, which everywhere stretch across the perivascular space, rather than with the bodies of the neuroglial

cells, which lie mainly at the peripheral boundary of the space, excludes all probability that the nerve fibres are for the innervation of these cells. Similar considerations apply to other cells with which the fibres and endings come into close physical relationship. Pigmentary cells and microglia, for instance, although found in crevices through the neurohypophyseal tissue, have a predilection for the vascular adventitia; only those in this latter situation are in the proximity of the nerve endings. The same applies to the epithelial cells migrated from the pars intermedia. It is unreasonable to think that such chance relationships have functional importance.

The swellings and masses found along the course of the perivascular nerve endings differ much from one another. Some are terminal, but many are not. Many variations in shape and size are found. Those of medium size are clearly situated within the perivascular space, though seldom if ever in intimate contact with the actual wall of the vessel. The position of the larger swellings is not so easily determined. The swellings take the form of sheets or ribbons of various shapes and are apt to be so large that they necessarily extend beyond the normal limits of the perivascular space. Sometimes it is difficult to be sure of the truly perivascular situation of these large forms, but from their structure and general relationships it seems most probable that they belong to the perivascular system of nerve endings. Certainly these large forms do not suggest nerve endings distributed to individual cells. Whether all these perivascular nerve endings, with their various swellings and masses, are usefully classed together can only be determined by further work in a variety of animals. The fact that the form most prevalent in the eminentia media, for example, is not the same as that which is most prevalent in the pars nervosa suggests that there may be functional differences to be discovered. Again the nerve endings found in the terminal meningeal corpuscles seem to possess some peculiarities of their own. At present all that is possible is to give a broad outline of the histological appearances.

The morphology of the nerve endings found in the perivascular spaces of the neurohypophysis suggests a close relationship to perivascular nerve endings of sensory character found in other parts of the body. The study of these was initiated by Dogiel with the description of what are now known as the Dogiel corpuscles. Our knowledge has since been extended by work on vascular innervation: in different organs (Sthör, 1922, 1932); on the carotid body and sinus caroticum (Castro, 1926, 1928); on the innervation of the great thoracic vessels and ductus arteriosus (Nonidez, 1941; Boyd, 1941), &c. These and other authors describe nerve endings

which they regard as sensory in nature and which both in their terminal course around the vessels and in the occasional presence of swellings, bulbs and terminal bodies closely resemble the nerve endings found in the perivascular spaces of the neurohypophysis. In particular Castro's (1926, 1928) description of the nerve endings in the carotid bulbs and carotid bodies of various animals show that these endings, in their perivascular position, in their various shapes and in their other characters are exactly similar to some of the nerve endings which are present in the neurohypophysis of the horse.

If further and final proof of the sensory nature of these neurohypophyseal nerve endings be demanded, it is to be found in the meningeal terminal corpuscle of the horse. Here is a structure evidently devoted to some specialized function, for it consists essentially of a dense mass of nerves and their bulbous endings. The bulbous endings are arranged in rich bunches which occur at the ends of the main fibres and of their short collateral branches. These specialized endings are so numerous and so large that they dominate the histological picture. The corpuscle forms a unit which is almost completely isolated from the pars nervosa from which it springs. Its structure is such that there can be no question here of innervation of either individual cells or more complex elements, for none of any importance is present; the nerve endings are not even obviously perivascular. Neither can there be any question here of artefacts or pathological changes associated with the presence or passage of migrating epithelial cells or their products. The unavoidable conclusion is that the corpuscle, in virtue of its nerve endings, must be devoted to some function which is of sensory character, and from this conclusion it follows that since the nerve endings of the perivascular spaces of the rest of the neurohypophysis are closely similar to those of the corpuscles, they too must be of sensory nature.

The meningeal terminal corpuscles present additional problems of their own. The fact that no nerve bundles are specially reserved for the service of corpuscles suggests that as yet the function of the nerve endings of these structures cannot have become very widely differentiated from that of the nerve endings in the perivascular spaces. As we have seen, the fibres which run into a corpuscle come from bundles which have already given terminal fibres to perivascular spaces. In what direction, if any, the sensory function of the meningeal terminal corpuscles of the horse may have become specialized we do not know. Indeed, why nerves and nerve endings should be concentrated at all in terminal corpuscles in this animal is unknown at present. In the rabbit there is no such concentration, and

even in the horse it is evident that whatever the specialized function may be, it is not one which cannot be carried out more or less efficiently within the substance of the pars nervosa. Right from the time the nerve fibres destined for a corpuscle can be recognized as they begin to gather at the periphery of the pars nervosa towards its apical region, they are seen providing large numbers of swollen bulbous endings exactly like those which characterize the corpuscle itself. The effect on the histological picture is seen in the occurrence of a distinctly noticeable accumulation of swellings and masses along the path of these fibres as they lie in the sheet close to the pars intermedia (Plate IV, fig. 11). One and the same fibre may be seen giving off collaterals with their bunches of bulbs and then entering the corpuscle there to repeat the process. But these are all problems of subsidiary importance. The main inference is that all these nerve endings observed in the neurohypophysis are receptors and therefore centripetal, not centrifugal, and that they are all, broadly speaking, of similar nature.

Of the fibres which enter the pars intermedia, those which end around its blood-vessels are the only ones of which we can speak with certainty. Morphologically these fibres are exactly like those found in similar situations in many other parts of the body and universally regarded as forms of centripetal vascular innervation (Plate VI, fig. 15). Lack of information makes it unprofitable to discuss the other fibres at length. Indeed, it would be rash even to venture an opinion as to whether there are two systems of fibres innervating the epithelium of the organ or only one. The system entering from the pars nervosa to ramify amongst the epithelial cells does certainly exist, and its meniscus-shaped and club-shaped swellings are not artefacts. The pericellular plexuses which other authors have described probably exist also, for we believe we have seen them in several preparations. The fact that in our hands these pericellular fibrils stain with such difficulty and so erratically suggests that they may possibly be different in character and function from those which come from the pars nervosa and stain so readily and precisely. There is the possibility that here is an example of the differential staining of two different nerve systems, but there is also the possibility—a greater one—that incomplete staining of a single system of fibres may be the explanation.

Function of the Neurohypophysis.

Facts described and discussed in previous pages indicate that the great mass of the neurohypophysis consists of sensory elements and that the main function of the organ must be that of one gigantic perivascular

receptive apparatus. Cajal (1911) came to the conclusion that the posterior lobe of the pituitary is sensory in character. He based his judgment upon the number and character of the fibres and upon the fact that he was able to find nerve endings amongst the epithelial cells of the pars intermedia. In spite of Cajal's eminence and his recognized genius for arriving at right conclusions, this opinion of his has been largely ignored and the work itself almost forgotten. Some later workers, observing again the unusual richness of the hypophyseal innervation, have, as is logical, expressed similar opinions. Thus Pines (1925) advances the idea that the posterior lobe has a special sensory and controlling rôle of its own; Roussy and Mosinger (1933*c*) admit the existence of some centripetal conductors although they regard most of the fibres of the posterior lobe as excito-secretory. Lhermitte (1938) mentioned observations, made in the course of surgical practice, which show that the stalk and neighbouring areas are highly sensitive.

But by far the most common view, specially since the spread of the modern hypothesis that the pars nervosa is an organ of special secretion, has been that the nerves of the neurohypophysis are centrifugal conductors. Anatomical support for the secretory hypothesis, so it is claimed, has come from studies of the neuroglial cells of the posterior lobe. The cells, as we have seen already, present certain peculiarities in morphological appearance which have been held to indicate obvious secretory function, and consequently, under the name of pituicytes, these cells have been regarded as affording firm anatomical support for the doctrine that the lobe as a whole is devoted to specialized secretory functions of immediate importance in the general bodily economy. But Griffiths (1940) has pointed out that the very characters which are claimed as showing the secretory nature of the pituicytes differ in no essential way from those found in neuroglial cells in general. Thus although conclusions drawn from studies of minute cell characters do not exclude the possibility that pituicytes may have secretory functions similar to those which, according to some authors, are possessed by neuroglial cells in general, they afford no support for wider claims. The granules are not peculiar to pituicytes and so cannot be used as evidence that pituicytes have peculiar functions. In particular this hypothetical secretory character of the granules does not of itself—and there is no other evidence—warrant the further assumption that pituicytes resemble secretory epithelium in function and are provided with nerves appropriate to such a function. A detailed description and discussion of the minute structure of the neuroglial cells of the neurohypophysis forms no part of the purpose of the present paper, but

an account has been given of the architectural relationships of these and other structural elements as they exist in the horse. Knowledge of such relationships gives confidence that these of themselves fully warrant the view that the real rôle of the pituicytes is entirely subsidiary to that of the nerve fibres and nerve endings. In fact the conclusion is reached that the function of these pituicytes is simply to clothe, support, protect and perhaps nourish the nerve fibres much as do the oligodendroglial cells of the central nervous system and the Schwann cells of the peripheral system which in many respects are the cells which pituicytes most closely resemble.

It has been claimed that the results of recent experiments made in the course of studies of diabetes insipidus prove that the neurohypophysis is a secretory organ of general importance. At first sight the experimental results do seem to bear the interpretation which has been so confidently put upon them but, without questioning the accuracy of the recorded observations, it is possible to adopt an alternative interpretation. The experiments referred to are, amongst others, those of Ranson *et al.* (1935, 1939); of Biggart and Alexander (1939) and, with less conclusive results, those of Gagel and Mahoney (1936); of Keller Noble and Hamilton (1936); of Mahoney and Sheehan (1936), and of Heinbecker and White (1941). These experiments show that section of the stalk is followed by diabetes insipidus. The generally accepted and seemingly obvious conclusion has been that section of the stalk interrupts a hypothalamic-hypophyseal system of efferent fibres directly controlling cells which secrete some anti-diuretic substance. An alternative interpretation is that the interrupted fibres are afferent and sensory and are connected with some central mechanism which controls the water metabolism of the body. This explanation fully accounts for the experimental results and in doing so removes some of the difficulties encountered when thought runs along accepted lines moreover, it is in agreement with the histological facts brought to light in the present paper.

As yet there have been too few careful anatomical studies of the effect which interruption of the stalk has upon those parts of the neurohypophysis which lie distal to the point of section or pathological lesion, but Fisher (1937), Keller *et al.* (1936), Rasmussen and Gardner (1940), Uotila (1939), Brooks (1938), Biggart (1936), Harris (1937) and some others claim to have demonstrated that in the posterior lobe there is, in addition to the degeneration of nerve fibres, a steady increase in the number of cell nuclei, which possibly represents a multiplication of microglial cells consequent upon the neural degeneration, and that finally there is a massive decrease in the number of pituicytes. This ultimate decrease in the number of

pituicytes is of considerable significance in relation to the theme of the present paper for it supports both the contention that the pituicytes are not secretory cells and the contention that these cells have a subservient, complementary relationship to the nerve fibres and indeed are simply neuroglial cells. Epithelial cells of the pars intermedia, which are of admittedly secretory function, neither degenerate nor decrease in numbers when the stalk is cut and, with it, all that part of their nerve supply which passes by way of the pars nervosa. Similarly with secretory cells in general, they do not degenerate or decrease in numbers when their stimulatory nerves are cut.

But though we must conclude from its structure that the neurohypophysis is primarily a sensory organ, this does not exclude the possibility that its sensory nerve endings may at the same time function to some extent as organs of internal secretion. Evidence is accumulating that such dual functions occur in other parts of the body. Wybaum (1936) and Ungar and Parrot (1938) have produced evidence that the antidromic vasodilatory activities of the perivascular sensory nerve endings are exerted through the medium of a humoral mechanism and Ungar (1938) has demonstrated that the electrical excitation of the second dorsal posterior root causes an increase in the oxytocic activity of the cerebrospinal fluid. The "vagus post-pituitary reflex" of Chang *et al.* (1937) may also be explained in a similar way; Pi Suñer (1941) has shown that the reflex is occasionally elicited by respiration of mixtures containing various amounts of CO_2 which presumably stimulate "chemoreceptors." Rasmussen (1938), whilst discussing the well-known fact that hormone-like substances can be obtained from the tissue of the neurohypophysis, remarks that "one is almost forced to assume that the hormones produced by the neural lobe are liberated without the intervention of secretory cells in the usual sense, as in the humoral mechanism associated with the sympathetic nervous system." If Rasmussen is right as to the source of the active substances it should cause no surprise to find a relationship between the pharmacological action of substances extracted from the neurohypophysis and substances liberated by the sympathetic and parasympathetic nerve endings. Acetylcholine, for example, has a well-known antidiuretic action (Pickford, 1939).

Studies of the morphology and architectural relationships of the nerve endings of the neurohypophysis give no certain indication of the particular stimuli which they normally receive and transmit. However, in view of the peculiar situation of the neurohypophysis, particularly of its close

proximity to the other lobes of the pituitary body and to the base of the brain, it seems most probable that the neurohypophysis may be a receptor of stimuli which enable the hypothalamic nuclei to exercise their exquisite control over the vegetative activities of the body. It seems possible indeed that the special function of the neurohypophysis is to detect changes in hormonal concentration and equilibrium—perhaps local concentration rather than general. Such a function would not be unique. In several situations in the body sensory nerve endings are known to have, or are generally supposed to have, as their function the detection of variations in pressure or composition of organic fluids. In the ependymal epithelium Laruelle (1934) has found sensory endings which are evidently closely similar morphologically to those of the neurohypophysis, and in the epithelium of the cavity of the neurohypophysis of the cat Collin and Fontaine (1936) have described spatulate or bulb-shaped endings of nerve fibres. The descriptions of Castro (1926, 1928), to whom our present knowledge of the carotid body is due, show that in this organ the nerve endings must be very similar to those of the neurohypophysis in both appearance and arrangement. Similar endings have been described also by Nonidez (1935, 1936) in the glomus aorticum and in the so-called "paraganglion aorticum supracardiale" for which this author, in view of its structure and probable functional relations, proposes the more appropriate name of "glomus pulmonalis." Similar endings have been found by Hollinshead (1941) in the abdominal bodies of mouse and rat. Analogies with this type of special organ do not end with richness in nerve fibres and perivascular nerve endings, combined with the small volume and apparent insignificance of the whole structure. In all, there are cells which, though they present characters suggestive of secretory activity, most probably have functions which are simply accessory to those of the nerve endings. There seem to be hormonal resemblances, too, for several authors have repeatedly tested the effect of extracts, mostly of the carotid body, and found them similar in action to those of some neurohypophyseal hormones (Bettencourt *et al.*, 1938). Castro, from his histological and physiological studies of the carotid body and carotid sinus came to the conclusion that these organs are adapted to the reception of stimuli initiated by changes in the pressure and chemical composition of the blood. The importance of these "presso-receptors" and "chemo-receptors" in the control of both respiratory and circulatory activity has been demonstrated in numerous studies which confirm Castro's original hypothesis. An excellent account of the literature of this kind of sensory reception by special organs is given by Schmidt and Comroe (1940).

In conclusion, then, the concise statement may be made that the opinion formed on the basis of the present work and of a consideration of the literature is that the neurohypophysis should be classed along with those organs, "chemo-receptors" and "presso-receptors," which are concerned in the detection of changes in the surrounding organic fluids. We believe that on account of its volume, situation and connections the neurohypophysis must be one of the most important of these organs and that possibly it plays an essential part in connection with the control of metabolic and hormonal functions which is exercised by the diencephalic centres in which its nerve fibres originate.

It is a pleasure to acknowledge special indebtedness to Dr. W. E. Gye, F.R.S., Director of the Laboratories of the Imperial Cancer Research Fund, not only for the initial suggestion that this study should be undertaken, but also for the generous hospitality and constant help without which the work could not have been carried through. Thanks and acknowledgments are also expressed to Mr. R. E. Glover, F.R.C.V.S., of of the Farm Laboratories of the Medical Research Council for the generosity he has shown in providing the ox and horse pituitaries used in the present work and for the trouble he has taken to ensure that the material was secured in perfectly fresh condition. Gratitude is also due to my colleague, Dr. W. J. Purdy, for invaluable help in the preparation of the manuscript, and to Mr. A. V. Cobbett, of the laboratory technical staff, for the care with which he prepared the photomicrographs used as illustrations.

Summary.

(1) The pars nervosa of the neurohypophysis of the horse has been the main object of study, particularly the nerve endings found in the organ. A number of facts have been established.

(2) The rather poorly developed fibrous capsule of the organ, the blood-vessels with their adventitial connective tissue, and the multitudes of nerve fibres may be regarded as the essential structural elements which, in combination, form the framework of the pars nervosa.

(3) The blood-vessels are everywhere surrounded by the perivascular space, a zone which varies in width, is comparatively free of cells, and is never encroached upon by the neighbouring nerve bundles, although these are often densely packed together in the intervening areas.

(4) The neuroglia is arranged in much the same characteristic manner as neuroglia elsewhere. The cell bodies lie closely applied to the surfaces which nerve bundles present to the perivascular space, and their slender

protoplasmic processes stretch directly across the space to end in the adventitia of the associated blood-vessel.

(5) At various points along their course, numerous isolated nerve fibres leave the bundles to end in one or other of three main sites, viz. (*a*) around the blood-vessels of the pars nervosa, where they crowd the perivascular spaces; (*b*) in the pars intermedia, where a large number end in relation to the blood-vessels; and (*c*) in the meningeal terminal corpuscles, which are sensory structures very rich in nerve endings. The corpuscles project into the fibrous meningeal tissue which lies at the apex of the pars nervosa near the point where the inferior hypophyseal arteries enter.

(6) All these terminal nerve fibrils of the pars nervosa are very much alike in type. Along their course and at their ends they show swellings, bulbs, clubs and meniscus-shaped masses. They are, in fact, similar in arrangement and appearance to the perivascular sensory endings found in other parts of the animal body.

(7) The very large number of nerve endings of sensory pattern found in the neurohypophysis forming, as for the most part they apparently do, a perivascular receptive apparatus leads to the conclusion that the nerves of the pars nervosa are mainly centripetal conductors and that therefore the pars nervosa is primarily a sensory organ.

(8) Neither the apparently casual nature of the anatomical relationship subsisting between neuroglia cells and nerve endings nor the size and morphological characters of the nerve endings themselves are features compatible with the hypothesis that the hypophyseal neuroglial cells of the horse constitute a specific gland of internal secretion innervated by any substantial part of the hypothalamic-hypophyseal system.

(9) In view of the analogies with terminal sensory apparatus found in organs whose acknowledged function is to detect variations in the composition and pressure of the blood, it is suggested that the ensemble of terminal sensory endings we have described in the neurohypophysis may constitute a "chemo-receptive" or "presso-receptive" apparatus devoted to the reception of stimuli which enable the hypothalamic centres to control the metabolic and hormonal functions of the body.

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EXPLANATION OF THE PLATES.

Only horse tissues are shown. Those in figs. 6, 7, and 17 were stained by Hortega's silver carbonate; all the others were stained by Cajal's silver nitrate method.

FIG. 4.—Proximal part of the pars nervosa. Shows how the blood-vessels lie in between the massed nerve bundles but always separated from them by the perivascular space. Running diagonally across the picture is a vessel (A) which has been cut longitudinally. Numerous terminal nerve fibres are seen entering the associated region of the perivascular space.

FIG. 5.—Distal part of the pars nervosa. Here the nerve fibres are arranged only in thin bundles and they, like the blood-vessels, run in all directions, irregularly. A, longitudinal section of a blood-vessel and its perivascular space. Within the space are very numerous terminal nerve fibres which run a twisting, tortuous course and present numerous swellings and bulbs, some of which are terminal. B, blood-vessel and its perivascular space cut transversely; terminal fibrils are also seen within the space.

FIG. 6.—Neuroglia of the proximal part of pars nervosa. The general arrangement of the neuroglial cells is well illustrated, particularly the way in which the cytoplasmic processes everywhere cross the perivascular space. A, longitudinal section of a blood-vessel; B, situation of the nerve bundles (unstained).

FIG. 7.—Similar to fig. 6 but higher magnification. Shows in greater detail how the neuro-hypophyseal neuroglial cells (A) lie closely applied to the surface of the

PLATE I.

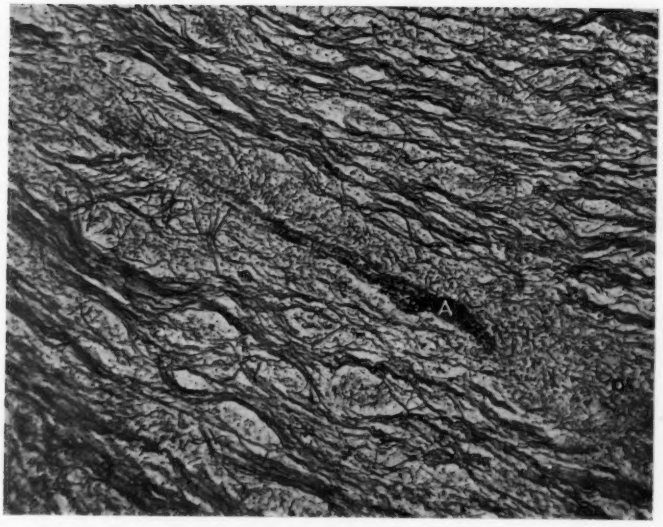

FIG. 4.

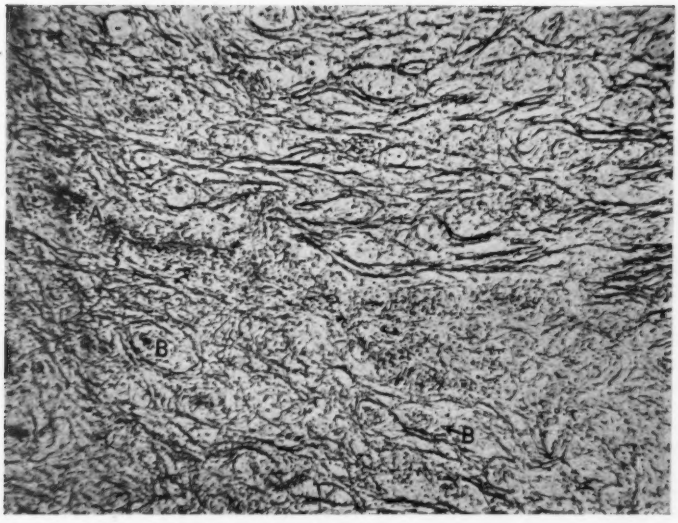

FIG. 5.

To illustrate article by E. Vazquez-Lopez.

PLATE II.

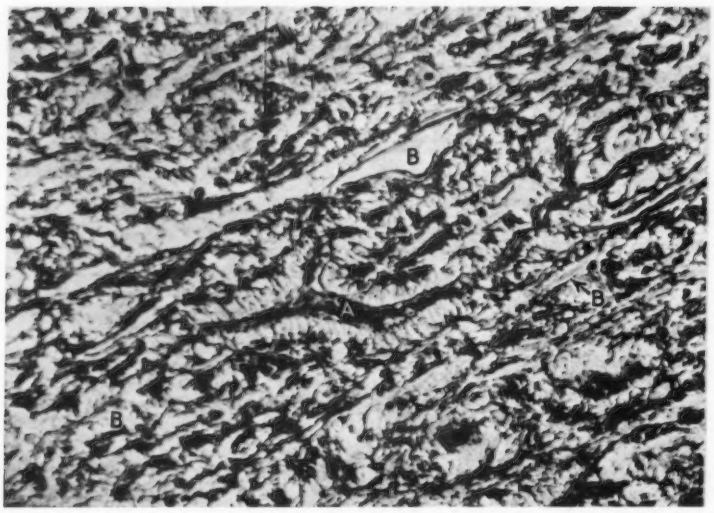

FIG. 6.

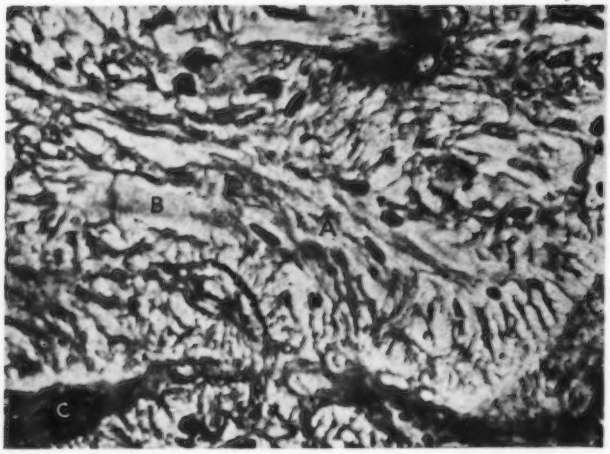

FIG. 7.

To illustrate article by E. Vazquez-Lopez.

PLATE III.

FIG. 8.

FIG. 9.

To illustrate article by E. Vazquez-Lopez.

PLATE IV

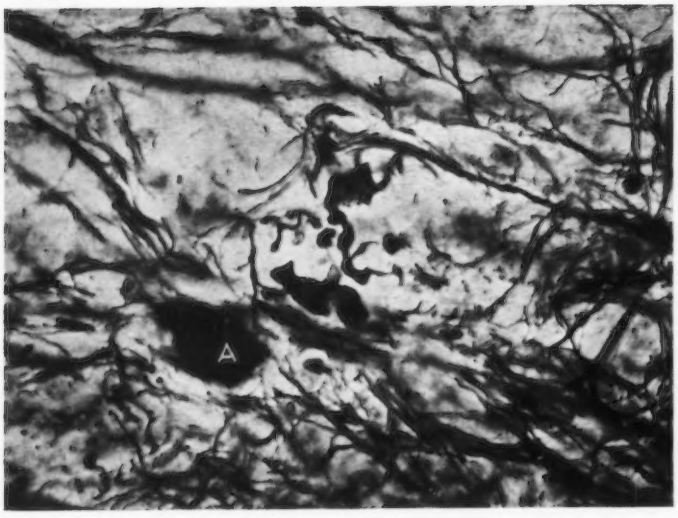

FIG. 10.

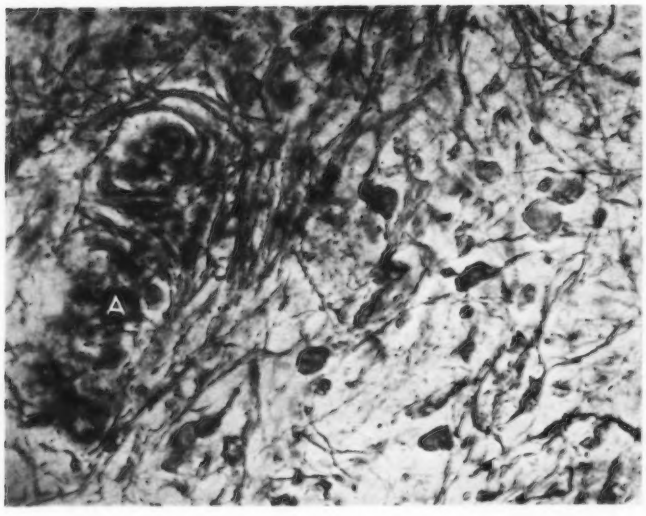

FIG. 11.

To illustrate article by E. Vazquez-Lopez.

PLATE V.

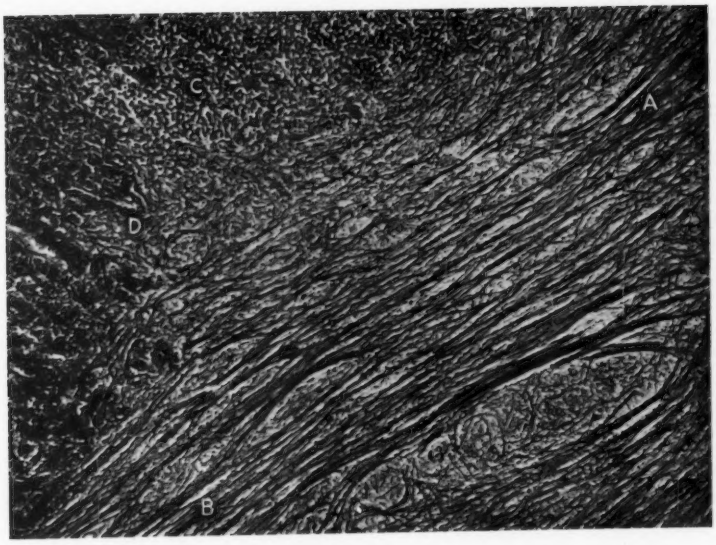

FIG. 12.

FIG. 13.

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PLATE VI.

FIG. 15.

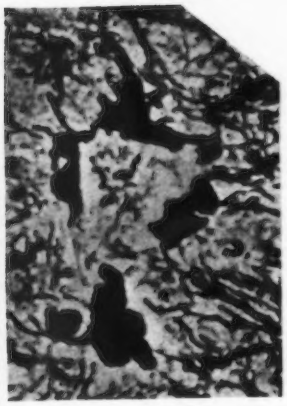

FIG. 14.

FIG. 16.

To illustrate article by E. Vazquez-Lopez.

PLATE VII.

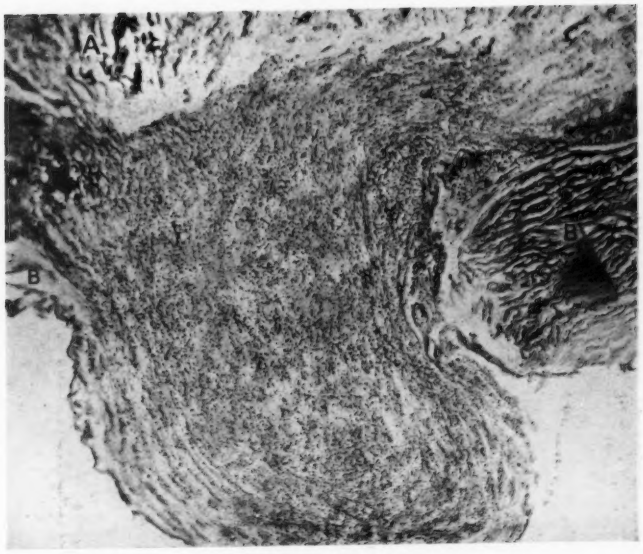

FIG. 17.

FIG. 18.

To illustrate article by E. Vazquez-Lopez.

PLATE VIII.

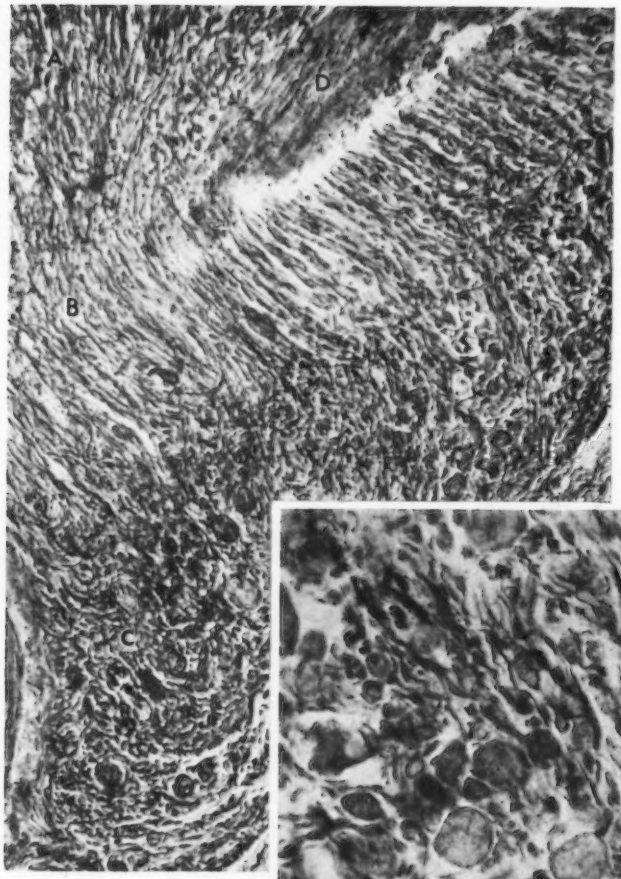

FIG. 19.

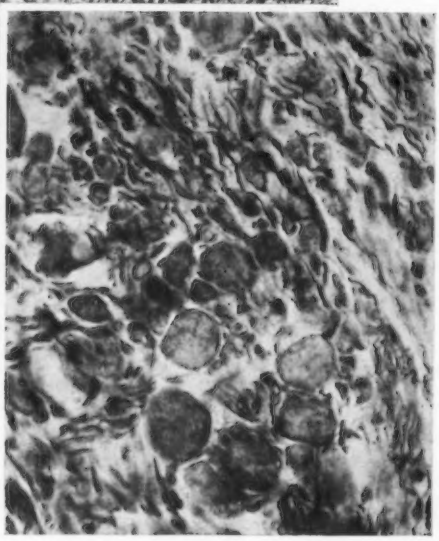

FIG. 20.

To illustrate article by E. Vazquez-Lopez.

unstained nerve bundles (B) and how their cytoplasmic processes stretch across the perivascular spaces to find attachment in the vascular adventitia (C).

FIG. 8.—Perivascular nerve endings in pars nervosa. High magnification. Running across the centre of the picture is a blood-vessel (A) which has been cut longitudinally. Within the corresponding perivascular space are seen terminal fibres (B) with swellings (C), bulbs and clubs (D) of medium size. (E) bundles of nerve fibres.

FIG. 9.—Perivascular nerve endings in pars nervosa. High magnification. Terminal masses of various forms—bulbs and clubs—are seen associated with the terminal nerve fibres. A, blood-vessel; B, bundles of nerve fibres.

FIG. 10.—Terminal bunch of swellings menisci and bulbs in a perivascular space of the pars nervosa. High magnification. A, terminal mass of great size, somewhat out of focus.

FIG. 11.—Medium sized bulbs, swellings and clubs of various forms in the peripheral part of the distal region of the pars nervosa. They lie near the pars intermedia (A) and are connected with nerve fibres which for the most part end in the terminal meningeal corpuscle.

FIG. 12.—Portion of the neurohypophysis where stalk (A) merges into the pars nervosa (B). The abundance of fibres (D) passing into the pars intermedia (C) is well illustrated. Some of these could be followed for some distance along their inter-epithelial course.

FIG. 13.—Border zone between pars nervosa and pars intermedia. High magnification. A, epithelial cells of pars intermedia; B, nerve fibre accompanying blood-vessel; C, bulbs and swellings of various sizes along the course of nerve fibres.

FIG. 14.—Bunch of very large terminal masses in the pars nervosa. They are so large that it is impossible to focus all parts sharply at the same time. Medium magnification.

FIG. 15.—Perivascular nerve ending in the pars intermedia near the pars nervosa. The nerve ending lies in the adventitia of the vessel and has the form of a bunch of bulbs and menisci. A, epithelial cells of pars intermedia. High magnification.

FIG. 16.—Peripheral zone of the stalk. Low magnification. Illustrates the fact that this zone, which is in contact with the pars tuberalis contains multitudes of thin terminal nerve fibres which run always in the outer part of the perivascular spaces. The zone contains no bundles of fibres. A, stalk; B, pars tuberalis; C, blood-vessels.

FIG. 17.—Meningeal terminal corpuscle. Low magnification. Shows how sharply the connective-tissue framework of the corpuscle is distinguishable from the substance of the pars nervosa. Many cell-nuclei are present. The clear spaces correspond in position to unstained giant bulbs and globoid nerve endings. A, pars nervosa; B, dura mater.

FIG. 18.—Meningeal terminal corpuscle showing the course of bundles of nerve fibres which come from the pars nervosa. A, pars nervosa; B, bundles of nerve fibres; C, dura mater lining the base of the skull. Low magnification.

FIG. 19.—Terminal meningeal corpuscle. High magnification. Numerous bulbs and globoid terminal masses are seen connected with the nerve fibres in their passage from the base (A) of the corpuscle, which lies within the pars nervosa, through the peduncle (B) and into the head of the corpuscle (C). D, dura mater.

FIG. 20.—Shows, highly magnified, giant bulbs and globoid structures which characterized the nerve endings of the meningeal terminal corpuscle.

THE SYSTEMIC NERVOUS AFFINITY OF TRIORTHOCRESYL PHOSPHATE (JAMAICA GINGER PALSY).

BY CHARLES D. ARING.

(From the Neurological Service and the Laboratory of Neuropathology, Cincinnati General Hospital, and the Department of Internal Medicine (Neurology), University of Cincinnati College of Medicine.)

One of the facets of the aptly termed "noble experiment," commonly known as prohibition in the United States, was the outbreak of paralysis which followed the use of Jamaica ginger extract[1] in the stead of the more palatable but discriminatively unobtainable liquors. This tragedy truly can be called an experiment, albeit an ignoble one, as it has furnished a ramifying medical and social problem for the twelve years that have followed its inception. The beginning was in March and April of 1930, when the paralysis appeared simultaneously in several localities. At the Cincinnati General Hospital, where the disease was introduced to me as a house officer on the neuropsychiatric service, more than 400 cases were observed during a six-month period. The inclusion of only thirty-three females and two negroes among these patients may reflect, if anything, the drinking habits of the sexes and races.

The disease was at first baffling, but as more and more persons came under observation with comparable findings, it became clear that we were dealing with a "new disease." The common denominator, so to speak, was the history, obtained in some instances eventually, of the ingestion of the extract of Jamaica ginger. That ordinary Jamaica ginger extract was of itself quite innocuous was definite, for many of the afflicted persons had been using it as beverage for several years.

Smith, Elvore and Frazier (1930), on the basis of chemical and experimental studies, announced that the substance in this Jamaica ginger

[1] "Fluid-extract of Jamaica ginger U.S.P.—alcoholic content 70 per cent.," had been dispensed to the public for many years. It was variously adulterated and evidently it served as a relatively innocuous, intoxicant beverage. It contained a small amount of the true oleoresin of ginger for flavouring. The substitution of triorthocresyl phosphate as an adulterant whose cost was less than that of other adulterants, resulted in the palsy. The Jamaica ginger extract contained about 2 per cent. triorthocresyl phosphate.

extract which caused the paralysis was triorthocresyl phosphate. This material apparently had been used as a denaturant in an inexpensive (tax free), alcoholic extract of the ginger.

Clinical Picture.

Because the condition known as Jamaica ginger paralysis was confined to certain localities in the United States, and was not encountered generally, it is thought that a short résumé of the clinical and pathological findings may serve for orientation.

On drinking the contaminated Jamaica ginger extract, many persons who had habitually used the substance noted that this lot tasted differently. Some of these imbibers immediately became violently ill, with abdominal cramps, nausea and vomiting. Many were afflicted with diarrhœa, which in some cases lasted several weeks. The usual lapse of time between drinking and the onset of neurological symptoms was from seven to fourteen days. The first indication of involvement of the nervous system was cramping, burning, stinging pain in the calves of the legs, and less often in the ankles and feet. Concomitantly, or shortly thereafter, numbness and tingling in the feet and legs developed, and this was followed, or accompanied, by weakness of the peroneal muscles, resulting in foot drop. The weakness progressed rapidly in severity and extent, and about one week after the onset of weakness in the lower extremities the hands became weak. Occasionally the latter weakness developed simultaneously with numbness of the hands and the patient became unable to perform the fine movements required in dressing, such as buttoning of clothing and tying shoe strings. The loss of power in the upper extremities progressed in extent and severity, and usually but not always, was limited to the muscles of the forearms and hands. By the time that wrist drop had supervened it was usual that the weakness of the lower extremities had progressed to such an extent that walking was impossible and the patient sought admission to the hospital.

The neurological abnormalities as recorded in 1930 were limited chiefly to the motor system and the reflexes. Atrophy was not an obvious early feature, and when noted, was limited usually to the small hand muscles and to the anterior muscles of the legs. The resistance of the muscles of the extremities to passive movements was reduced. There was paralysis of the muscles subserving the movements of the toes and ankles. Usually there was some weakness of movement about the knee-joints and of all movements of the thighs on the trunk. Movements of the fingers and

hands were usually impaired in different degrees, those especially affected were extension of the fingers and of the hands. The muscles of the arms were not as severely involved as the distal muscles, and the muscles of the shoulder girdles even less so. The more severely affected patients had weakness of the abdominal and lumbar muscles (about 25 per cent.). Sensory changes varied from patient to patient. In many sensation was reported to be normal. Tenderness was found along the nerve trunks or in the muscles of the legs and feet, in about half of the cases where it was tested. In some, mild impairment of pain, temperature and touch was recorded, of an extent ranging from the soles of the feet to the whole of the four extremities. In a few there was noted, loss of the appreciation of vibration in the feet, or below the knees. In a small number hyperæsthesia was found in the feet and legs and in an occasional case in the forearms, hands, legs and feet. The report of the sensory examination was inadequate in the majority of the records, and since I participated in many of the early examinations, it may be noted that the evaluation of sensation was extremely meagre. Usually this inadequacy may be assumed when a "purely motor polyneuritis" is said to have been found. The tendon reflexes were normal, with the exception of the ankle-jerks which were never obtained, and of hyperactive knee and arm reflexes in the occasional case. The abdominal and cremasteric reflexes were normal, and there was no response to plantar stimulation. The hands and feet were almost invariably cold, moist, and cyanotic. There was involvement of the sphincters in sixteen patients. The cerebrospinal fluid examination and other laboratory studies were normal (urine, blood counts, hæmoglobin determination, blood chemistry, and culture).

The weakness, whatever its distribution, usually progressed until about two months after the onset. Pain in the legs was a common complaint up to that time. The severity of the affection may be judged by the fact that the majority of patients became unable to feed themselves because of weakness in the upper extremities. There then occurred the beginning of a very slow improvement in strength and remission of the pain. The patients were allowed to walk as soon and as well as they could, some were given Gowers' boots, and in some an arthrodesis was done at the ankle to overcome the foot drop. In most instances attempts were made to dispose of these patients to chronic hospitals, poor houses, and to their homes. Interest waned as the patients were seen in increasing numbers, and after the cause of the disorder was determined to be triorthocresyl phosphate, the disease was classed among the chemical neuritides and for the most part forgotten.

Pathological Picture.

Vanderahe (1931) and others (Kidd and Langworthy, 1933; Smith and Lillie, 1931) described the pathological changes which they found in the nervous system. In one case where death followed bulbar palsy fifty days after the onset of weakness of the extremities, and in others, where death was caused by complicating factors and not by the paralysis, there was scattered myelin degeneration in the radial and anterior tibial nerves, and in the anterior roots of the lumbar and cervical cord. Swelling, chromatolysis and nuclear eccentricity were the characteristic changes found in the anterior horn cells of the spinal cord. Other cells were pyknotic. Varying numbers of amyloid bodies were present in the spinal cord. There was little or no reactive cell change and no signs of inflammation. In the uncomplicated case, dying from bulbar palsy, study of the serial sections of the medulla revealed central and diffuse chromatolysis in the dorsal motor nucleus of the vagus, the hypoglossal nucleus and the nucleus ambiguus. There were numerous degenerated myelin fibres in the roots of the vagus nerve. No other case of acute bulbar palsy has been recorded in triorthocresyl phosphate poisoning.

In summary, the disease was manifested clinically as a severe polyneuritis with disability especially evident in the motor functions. Pathological studies complemented the clinical findings, the lesions were limited to the nerves, and the anterior horn cells of the spinal cord, and in one instance to the motor cells in the medulla. The evidence seemed rather complete that triorthocresyl phosphate poisoning resulted in a neuritis.

There then occurred a hiatus during which these people were seen at a distance in the Chronic Hospital and in the wards at the Cincinnati General Hospital. There is some evidence that a few of the patients made a rather good recovery. It is a clinical impression that in a group not markedly endowed with ambition or energy, a few of the patients made desperate efforts to resist their disease. After the period of pain had passed (about two months after onset), and even before, they arose from their chairs and beds, and stumbled about the hospital wards and grounds with the aid of canes, crutches, and chairs, attempting to exercise their crippled extremities. The patients who worked the hardest appeared to make the best recovery, though it is apparent that those who tried may have had the least neurological damage. It was unusual, where an accurate history could be obtained, to find the severity of the paralysis related directly to the amount of contaminated ginger drunk. Those patients who were admitted to the wards of the hospital all exhibited profound

neurological signs, apparently of a comparable degree of severity. Some of the tissues from a recovered case have been studied, and will be described later.

Indications that the Disease Involves the Spinal Cord.

During the intervening years a number of patients afflicted with the palsy caused by triorthocresyl were admitted to the Cincinnati General Hospital because of various medical problems unrelated to their paralysis. Signs of involvement of the pyramidal tracts were recorded in the majority of them, but no one commented on these progressive neurological signs until 1936, after some of these cases were examined pathologically. Re-examining the original records it becomes evident, on second sight, that there was indication of damage to the pyramidal tracts on the admission examinations in 1930 in some instances. In 37 of 316 patients, the patellar reflexes were recorded as hyperactive. A not uncommon complaint was that of spasmodic involuntary contractions of the legs, usually noted as "violent jerking which awoke the patient." This complaint was volunteered by patients and was recorded in the nursing notes anywhere up to five months after the onset. Merritt and Moore (1930) recorded signs suggestive of pyramidal tract damage in Jamaica ginger palsy. In several cases they recorded involuntary flexor withdrawal of the palsied leg from stimulation of the plantar surface of the foot. They suggested the possibility that the pathological process was not confined entirely to nerves but might involve the cord to some extent.

Later three new cases of triorthocresyl phosphate poisoning were examined with better insight. These persons developed the palsy after imbibing some of the contaminated Jamaica ginger found stored away in a basement. The cache had been uncovered by the receding waters of the 1937 flood of the Ohio River, and the men involved were painters who were at work renovating the building. Five persons participated in disposing of a case of "fluid-extract of Jamaica ginger alcoholic content 70 per cent." (about one hundred two-ounce bottles), and all were afflicted with the paralysis. A careful neurological examination was made on three of these people who were admitted to the hospital, and a daily check was made to determine when the signs of involvement of the spinal tracts made their appearance. A case history of one of the patients is illustrative.

A 29-year-old white man was admitted to the neurological service of the Cincinnati General Hospital on September 8, 1937. Four weeks before entry he had drunk four bottles (eight ounces) of Jamaica ginger extract. Two weeks later he noted cramping pain in the posterior aspect of his legs and in his feet, and the next day

he developed numbness and tingling of the feet and toes and bilateral foot drop. On September 3, his fingers became numb and somewhat weak. The weakness of his hands and lower extremities progressed very rapidly and he was unable to walk at the time of admission to the hospital on September 8.

Abnormalities found on the admission examination were limited to the nervous system. The cranial nerves were normal. There was fairly marked atrophy in the muscles of the thenar and hypothenar eminences, and in the lumbrical and interosseous muscles of the hands. At rest the fingers were held in a semi-flexed attitude. There was some atrophy of the flexor and extensor muscles on both forearms, and in the small muscles of the feet, and, the peroneal and anterior tibial muscles of the legs. The gastrocnemius and soleus muscles were small and flabby. Adduction and abduction of the fingers were not possible, and he was unable to approximate the thumb to the third and fourth fingers of either hand. All movements of the hands were very weak, flexion of the forearms on the arms was just possible. There was weakness in extending the right forearm, but not in extending the left. There was moderate weakness of both deltoid muscles. The umbilicus elevated slightly on raising the head from the bed. There was bilateral pes cavus and the feet rested in plantar flexion. No voluntary movement was possible in the toes or about the ankles. The power of the quadriceps muscles was good, although obviously somewhat weakened, and the hamstrings were quite weak. Extension of the thighs on the pelvis was strong, while flexion was weak. The gluteal muscles were weakened slightly. The resistance to passive movement was diminished in all of the extremities, but it was impossible passively to extend or flex the knees completely probably because of beginning contracture about these joints. The patient complained of numbness and tingling in the toes and feet. There was tenderness to deep pressure in the leg and thigh muscles. Pain in the feet was evoked by stimulation of the plantar surface with a wood applicator. There was slight loss of sensations of touch, pain, and temperature below the knees, sensation approached normal at the knees (soft border). The appreciation of vibration and passive changes in the position of the toes was normal. No sensory abnormality was detected in the upper extremities. The appreciation of the size, shape, form and texture of objects, figure writing and two point discrimination was normal. The tendon reflexes in the upper extremities and the knee-jerks were normal, the ankle-jerks were not obtained. The abdominal and cremasteric reflexes were normal. There was no response of any kind to plantar stimulation.

The hands and feet were drenched with cold sweat on a warm day. Vascular studies (oscillometric record of temperature changes) indicated that there was some vasospasm in the skin of the lower extremities. This was thought to be the case because of the following temperature readings (in degrees centigrade):

	Before heating	*After heating*
Temperature at various points on the toes ...	23·5 to 24	31·5 to 33
Temperature at various points on the feet ...	24 to 25	33·5 to 34·5
Temperature at various points on the legs ...	28 to 30	34 to 35·5
Temperature at various points on the thighs	30·5 to 34·5	34·5 to 35·5

The temperature difference in the upper extremities before heating and after two hours of heating was about 1° C. in the hands, and between 2° and 3° in different regions of the arms. There was no measurable change of temperature in the various areas of forearms before heating and after two hours of heating.

The knee reflexes disappeared on September 21, thirteen days after admission to the hospital. The knee-jerks returned on September 23 and

were hyperactive by October 1. Somewhat the same development of signs suggesting the possibility of pyramidal tract involvement occurred in the two other patients with the comparatively recent triorthocresyl phosphate poisoning, both of whom had the same history and were admitted to the hospital on September 8, 1937. One man, the father of the patient described above, developed markedly hyperactive knee-jerks and patellar clonus on October 21, 1937, six weeks after admission to the hospital. His knee-jerks had been normal previously. The third man, a cousin of the patient described in detail, had hyperactive knee-jerks on admission to the hospital and developed involuntary flexor spasms of the lower extremities on October 1, 1937, twenty-three days after admission to the hospital. On October 10, stimulation of the soles of the feet resulted in strong reflex flexion at the knee, whereas voluntary movement about that joint was extremely weak. It might be mentioned in passing that large doses of vitamin B_1 had no effect on the course of the disease in these three persons. In consideration of this clinical evidence, it seems probable that the pyramidal tracts in the cord are involved early in triorthocresyl phosphate poisoning in man.

Present Status of Patients with Jamaica Ginger Palsy.

More than one hundred patients have been examined in the late stage of the palsy over the past five years, some of them repeatedly. The usual story after the advent of the paralysis was of a gradual return of strength over several months until a stationary stage was reached, usually a year or more after the onset of the disease. The upper extremities improved more rapidly and to a greater degree than the lower. The ages of the patients examined during the late stage of the disease ranged from 33 to 75 years. The neurological signs differed in no essential in the young and aged. The cranial nerves presented no abnormal signs. The patients walked with the aid of two canes. The gait was of the spastic type, the toes dragged on the floor (foot drop) and one foot was thrown in front of the other, in scissors fashion. Atrophy of muscles was generalized in the extremities, but much more obvious in the distal than in the proximal muscles. The hands were "clawed," the fingers resting in the position of moderate or extreme flexion. The foot had assumed the shape of that usually associated with Friedreich's Familial Ataxia. The arch was high and the proximal joints were fixed in moderate dorsiflexion, the distal joints in extreme plantar flexion. There was contracture of the Achilles tendon. Despite the atrophy and deformity of the hands the grip usually

was strong. Extension of the fingers and hands was weakened slightly. There was bilateral foot drop and inability to move the ankles and toes through more than a 15 to 25 degree arc. Movement about the knee-joints though reduced in vigour, was strong, movements about the thigh joints was not measurably affected. The resistance to passive movement of the lower extremities was increased, especially in the adductors of the thighs. Usually there was found a stocking type of hypoæsthesia (touch, pain, temperature, tickle) in the lower extremities with a soft border about the knees. Sensation in the upper extremities sometimes was affected similarly, but to a lesser degree. Deep pressure in the feet and calves sometimes caused tenderness, and the patients usually could not tolerate the stroke of an applicator on the dorsal or plantar surfaces of the feet because it caused a sensation of "cutting and burning" which was delayed in onset and in termination ("afterglow"). The usual diminution in the appreciation of vibration was more than would be accounted for by the age of the patients. The tendon reflexes were hyperactive. The ankle-jerks were not obtained in about 20 per cent. of cases, but when present their elicitation resulted in sustained clonus. Patellar clonus was common. The plantar responses were usually strongly extensor. When the toes were paralysed no response was elicited. The feet were cold and wet, and showed a dusky, reddish, mottled cyanosis.

Late Pathology.

The pathology of triorthocresyl phosphate poisoning will be summarized only, as it is to be the subject of a detailed analysis in another paper. Material is available from thirty-six patients who suffered from this disease.

The pathology may be divided for convenience into the neural and the extraneural. Including somatic musculature with the former for convenience, it is found that the main neural lesions are in the muscles, nerves and spinal cord. Marked degenerative changes were found in the muscles of the limbs. The degeneration comprised rather spotty loss of muscle fibres and replacement by connective tissue and fat. The small arteries, and particularly the capillaries and pre-capillaries of muscle, were involved in a process, which because of thickening of all of the coats of the vessels had extremely narrow lumina. The intima was involved to a greater degree than the media and adventitia. The larger arteries were relatively normal. Degeneration in the muscle could be related to the affected vessels with narrowed lumina in more instances than not. Accumulations of fat were found within the parenchyma of the muscle, a relatively intact

fibre might end in a string of fat cells, and an entire segment of the muscle might be replaced by fat. Fibres which retained their identity usually retained their striation, though these sometimes faded out along the longitudinal course of the fibre. There were degenerated areas in the muscles which had been replaced by fibrous tissue composed of a coarse mesodermal reticulum which stained red in hæmotoxylin and Van Gieson preparations. In these areas there were large numbers of capillaries which sometimes had an angiomatous appearance. The walls of these capillaries were markedly thickened. Their varying size, shape and degree of development, some without lumina, support the thought that this process represented a new formation of capillaries, an unusual form of reactive compensation in response to an insufficient blood supply. This reparatory process might be compared to some extent with that of the formation of callus in bone repair.

In all cases there was found evidence of degeneration in whatever nerves or roots were exainined. Axones were of irregular width and decreased in number. There was a severe patchy loss of myelin in the nerves. There was a heavy overgrowth of connective tissue in the nerve trunks (perineurium and endoneurium). This proliferation was reminiscent of that described in the hypertrophic neuritis of Dejerine and Sottas, a factor on which probably depended the clinical irreversibility of the peripheral neuritis. The same capillary fibrosis that has been described in the muscles was present to a somewhat lesser degree in the nerves.

In the spinal cord the leptomeninges were always thickened, though there was little nuclear increase. Degeneration in the white matter varied in severity from case to case, but was invariably present. There was no exception to the involvement of the lateral pyramidal tracts. This degeneration was most severe in the lower segments of the cord, and was not found above the upper segments of the spinal cord. The myelin of the direct pyramidal tracts usually appeared to be affected, but this may be part of the rim of degeneration that encircled the cord. This "rim of degeneration" resembled the vacuolated type most often seen in subacute combined degeneration. The lateral pyramidal degeneration, on the other hand, was unlike that of subacute combined degeneration in that it was not vacuolated, and there was an intense gliosis in the degenerated area. The tract of Goll (fasciculus gracilis) was involved moderately in many of the cases, the tract of Burdach was never affected. Glial replacement was obvious in the tract of Goll. This degeneration was most obvious in the upper segments of the cord. In some instances the involvement

of the tract of Goll was very slight and was confined chiefly to the white matter just dorsal to the grey commissure. In an occasional case the posterior columns were intact. The degeneration of white matter always stopped short of the medulla; in no case was there white matter degeneration in the cerebrum.

In the grey matter of the anterior horns many of the nerve cells were affected. The nerve cells were present in markedly reduced numbers. Those remaining were pyknotic, and many had lost the outline of nerve cells. In some there were collections of fat and Nissl substance was sparse. There was an obvious increase in glial nuclei in the grey matter. These changes were most obvious in the anterior horns, but they had occurred to a certain extent in the lateral horns as well. The segments in which the grey matter was most severely involved were the lower dorsal and upper lumbar.

A minor degree of neuronal change had occurred in the brain-stem and cerebrum, but in no case was the loss and deterioration of nerve cells obvious as in the spinal cord. The leptomeninges of the cerebrum were thickened.

The blood-vessels of the spinal cord showed homogenization and slight thickening of the wall. In one patient, aged 35, thrombosis of the capillaries were observed in the commissure. The vessels of the brain revealed little abnormality.

The capillary lesions described in the musculature were found in many of the viscera. The entire gastro-intestinal tract was affected by the hyperplastic fibrosis. The ages of the patients at death were 34, 35, five were between the ages of 42 and 47; eleven between the ages of 51 and 59; ten between the ages of 61 and 68; six between the ages of 70 and 79, and 81 and 88. The man who died in May of 1930 at the age of 34 died of an acute endarteritis, particularly marked in the lungs, where there were numerous infarcts. In twenty-two of these persons death was attributable directly to arteriolar disease.

The histological study of the tissues of one of the patients who "recovered" from the palsy should be mentioned.

A patient was observed at the age of 54 in the hospital wards from March 26, 1930, to December 3, 1930. He had been imbibing Jamaica ginger for eleven years on the average of a bottle (two ounces) per day, the last indulgence having been on February 24, 1930. He had had the typical palsy of the upper and lower extremities. He was able to get about on admission, but his lower and upper extremities gradually became weaker until late April when there began to occur a slow return of strength. By early May he was assisting with the lighter work on the ward. The extremely slow improvement continued, and at the time of his discharge in December he was walking well.

At 63 years of age he had a few neurological signs, which were recorded for the last time five months before his death from cardiac disease. There was slight muscle atrophy in the hands and feet, all the movements of the toes were reduced in strength, and especially affected was dorsiflexion of the great toe which was barely possible. Dorsiflexion of the feet was weakened, but otherwise the strength in the lower extremities was normal. He was confined to bed because of cardiac failure and the gait was not tested, but the patient stated that it was normal. The appreciation of vibration was lost below the level of D-10, and touch and pain were diminished below the knees. The feet were hypersensitive to applicator stroke, there was no tenderness of the muscles to deep pressure. A weak left extensor response was obtainable by Chaddock's procedure.

The histological abnormalities in the nervous system were limited to the spinal cord. Slight demyelination of the column of Goll had occurred throughout the cord, and was most obvious in the cervical segments. There was a rim of comparatively light staining of myelin sheaths about the circumference of the cord. There was a striking loss of anterior horn cells, and obviously deterioration had occurred in many of those that remained (distortion, loss of Nissl substance and nucleoli, and accumulation of fat in the scarlet red stains). The neuronal changes were most severe in the cervical and thoracic segments. The leptomeninges were thickened. The lesions in the peripheral nerves were not marked. There was some swelling of the myelin sheaths. There was no fibrous proliferation and no changes in the blood-vessels of the nerves. On the other hand, practically all of the small arteries of the viscera were affected by endothelial proliferation.

Discussion.

The routine examination of Jamaica ginger palsy of itself has little value. An analysis of the implications which the disease offers is at once interesting and informative.

From a clinical standpoint the disease superficially resembles amyotrophic lateral sclerosis if one allows for the precedent neuritis, though neuritis in the lower extremities has been recorded initially in the syndrome of amyotrophic lateral sclerosis (Wechsler, Brock and Weil, 1929). While only one patient with Jamaica ginger palsy died of bulbar palsy, the rarity of this manifestation may be related directly to the limited amount of the exogenous toxin ingested. The peculiar taste of the contaminated batch of ginger and the truly terrific gastroenteric upset that its ingestion caused induced these people to desist immediately from using more of it, or to turn to another more palatable brand. It may be therefore that those afflicted did not get enough of the poison to reach the bulb, so to speak. The single patient (aged 59) who died of bulbar palsy (Vonderahe, 1931), on the other hand, appears to have been unique in that over a longer period than was usually the case, she seems to have taken about ten to fifteen times the amount of the poison ingested by the ordinary patient. She died fifty days after the onset of neurological signs, unable to talk or to swallow. The resemblance to amyotrophic lateral sclerosis

is furthered by the study of animals given triorthocresyl phosphate (Kidd and Langworthy, 1933; Smith and Lillie, 1930). Their death resulted eventually from bulbar palsy or from cachexia. In animals the drug appears to poison to death by accumulation; it is eliminated very slowly, if at all.

In man the final histopathological picture has some resemblance to that of amyotrophic lateral sclerosis. The nerve cell change in the spinal cord, as well as the pyramidal tract degeneration, might be considered to be similar. Posterior column affection has been recorded in amyotrophic lateral sclerosis (Davison and Wechsler, 1936). However, the pyramidal tract degeneration stops short of the medulla and the cerebral hemispheres are intact. This might represent a function of the ingestion of a limited amount of the toxin. It is unnecessary to labour the point further, but the superficial similarity of some of the features of the two diseases should be brought forward and thought about.

One might also invoke "pathoklisis" (Vogt, 1925) and note that systems that belong together functionally share an affinity for various destructive agents. While it might be said that Jamaica ginger palsy, with its severe affliction of various motor mechanisms (pyramidal tracts, anterior horns and their axones), lends some support to the theory of pathoklisis, it must be said also that it does not clarify the mechanism one whit.

In consideration of the severe involvement of the small arteries and capillaries by triorthocresyl phosphate it might be enlightening to turn from pathoklisis to lessened arterial supply as a causal factor. This procedure might be called the method of Spielmeyer (1931), who stressed the importance of local blood supply in local vulnerability.

The latent period between ingestion of the poison and the development of early neurological signs, and the period which passed before the signs reached the maximum, might represent the time required for the development of the endothelial proliferation with consecutive narrowing of the capillaries. The neurological signs may have developed when the vessel, owing to the narrowing of its lumen, was no longer able to deliver sufficient or suitable nutriment to the nervous tissue to maintain adequate function, the latter probably depending somewhat on the activity of the person afflicted. In the muscles and nerves there is no reason to doubt that this mechanism was operating, since the degenerations therein can, in many instances, be related morphologically to the proximity of an afflicted vessel. Where the vessel escaped so did that portion of the muscle, and even to a certain degree that portion of the nerve.

The degenerations in the cord are more difficult to relate to insufficiency of the blood supply. The involvement of important radicular arteries in the lumbar region might be postulated, since the column of Goll in the posterior columns was involved as well as the pyramidal tracts. The latter were most severely involved in the lowest segments, and the degeneration became less as one examined the cord in an ascending manner. Since the tract of Goll takes origin from the dorsal root fibres entering the lower segments of the cord, and since the pyramidal tract seems to have degenerated in retrograde fashion, it appears possible that the chief noxa affected the lower cord segments.

The fact that the tract degeneration stopped short of the medulla, as it does in subacute combined degeneration is probably significant. If the vascular insufficiency hypothesis holds in Jamaica ginger palsy, it might throw some light on the mechanism of cord degeneration in subacute combined degeneration. It is interesting that there was a tendency as recently as twenty years ago to associate subacute combined degeneration of the cord with "septic conditions of the gastro-intestinal tract" (Buzzard and Greenfield, 1921). In subacute combined degeneration the vessel walls may show fatty and other degenerative changes in those parts of the cord most severely affected. The maximum change in the spinal cord is to be found in the mid-thoracic region, at the level where the blood supply to the spinal cord is least rich. Browder and Meyers (1941) have submitted some evidence that the "spongy state" found in the cord associated with epidural abscess may be due to impairment of the intrinsic circulation.

It is a remarkable fact that the brain, including the brain-stem, is minimally involved, if at all, in triorthocresyl phosphate poisoning. This escape would seem to be related somehow to the lack of involvement of the capillary system of the brain. A reason for the distribution of the capillary fibrosis in the viscera, muscles and nerves, and only slightly in the spinal cord, and not at all in the brain is not clear. Possibly the aid of the "blood-brain barrier" might be invoked if our information was a bit clearer on this mechanism.

The relationship of triorthocresyl phosphate poisoning to thromboangiitis obliterans should be mentioned. The predominant incidence of both diseases in the male, and the striking similarity of the late histopathology of both conditions are suggestive. Clinically the patients with Jamaica ginger palsy, practically without exception, had vasomotor abnormalities in the feet. In two cases a high amputation of the thigh had to be done for gangrene, which developed eight years after the incep-

tion of the disease. In addition, the early signs of triorthocresyl phosphate poisoning are similar to those of thromboangiitis obliterans.

There remains for consideration the latent period between the ingestion of triorthocresyl phosphate and the development of neurological signs. This constant factor, amounting to about seven to fourteen days in the human subject, and to a comparable time in animals, depending on the species and the dose of the poison, has been remarked on by all who have dealt with the disease. The possibility that this time interval is required to initiate the capillary endothelial proliferation has been mentioned previously in the discussion. At present we are trying to alter this latent period in animals, in an effort to determine what structures may be responsible for the protection of the body against such poisons. The study of the pathology of triorthocresyl phosphate in man and animals is being continued in the light of the interpretations set forth in this discussion.

Summary

Jamaica ginger palsy (triorthocresyl phosphate poisoning) is described clinically and pathologically. The disease is essentially a hyperplastic fibrosis of the smaller arteries and capillaries, which appears to begin to develop in the latent period (about fourteen days) between the ingestion of the poison and the appearance of neurological signs. The degenerations in the muscles and nerves can be related to some extent to contiguously affected capillaries. An attempt is made to explain the degenerations in the central nervous system (nerve cells, pyramidal tracts and columns of Goll in the spinal cord) on the same basis. Resemblances between triorthocresyl phosphate poisoning and amyotrophic lateral sclerosis, subacute combined degeneration, and thromboangiitis obliterans are mentioned with reserve.

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THE ANATOMY AND PHYSIOLOGY OF CUTANEOUS SENSIBILITY: A CRITICAL REVIEW.

BY F. M. R. WALSHE.

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I.—Introduction.

Nearly forty years have elapsed since the publication of Head and Rivers' paper, "The Afferent Nervous System from a New Aspect" (1905), opened a fresh chapter in the study of the sensory system, and gave a direction to subsequent studies and to our ideas on the subject that still remains dominant in neurological thought. Prior to Head's work there had been two main trends in the study of the sensory nervous system: purely physiological and morphological studies of the sensory end-organs in normal skin and of their functional qualities, and the predominantly anatomical studies of sensory nerve distribution in lesions

produced by injury and disease. Head, feeling that the study of disordered sensory function had been subordinated to anatomical considerations and that it called for the same physiological methods that had been devoted to the study of normal cutaneous sensibility, turned to the investigation of the nature of sensory disorders and to their interpretation in terms of normal function: at first as revealed in the clinical examination of the results of disease and injury of peripheral nerves, and later by the experimental method. As is well known, he caused a cutaneous nerve to be severed in his own forearm, and then with his collaborator Rivers proceeded to examine and analyse the disorders of sensory function immediately resulting, and to trace the restoration of sensory activity as the severed nerve regenerated. The method was essentially a physiological one, its prime object the determination of function. It was only secondarily concerned with structure.

In seeking to generalize from his observations, he came to postulate the existence of a double system of cutaneous sensory nerves and end-organs to which he gave the now familiar names of the protopathic and epicritic systems. His studies included no direct attempt to ascertain whether or not the skin actually contained these anatomical mechanisms, but it was concluded that these must exist to account for the physiological phenomena observed. The later and more exhaustive studies of Trotter and Davies (1909-13) on the sensory innervation of the skin were carried out by the same experimental method: namely, by cutaneous nerve sections on the observers themselves, but they did not find it necessary in the interpretation of their findings to postulate the existence of any anatomical structures not already known to exist. Still later, Boring (1916) again adopted this experimental method. and here, as in the two earlier series of observations the prime concern was to determine the nature of cutaneous sensory function rather than that of sensory structures.

More recently, Lewis (1936) has used the experimental method in the investigation of the sensory phenomenon of cutaneous hyperalgesia produced by local injury. Like Head he has deduced the existence of a special system of nerves and end-organs in the skin to account for his findings and these he has named "the nocifensor system of nerves." Although he specifically denies strictly sensory functions to these nerves, he associates them closely with the activity of sensory nerves, and therefore they may be considered here. Like Head, too, Lewis provided no direct evidence of the actual anatomical existence of the system of nerves in question.

Therefore, both these observers may be said to subordinate the study of structure to that of function, and are ready to call into existence, as it were, anatomical structures to meet the apparent requirements of physiological observation. At a time when the state of knowledge of the sensory equipment of the skin was imperfect, this mode of deduction was perhaps justifiable and necessary, and it has certainly added valuable chapters to the body of neurophysiology. Yet there are manifest dangers in the method, for theories of function can never be regarded as soundly based until they rest upon an assured foundation of ascertained structure.

It is important to note that the structures the existence of which has been postulated by Head and by Lewis are peripheral and not central. In the case of Head's theory of the constitution of the sensory system, the progressive elaboration of this system during phylogenetic evolution is believed to have been achieved by the multiplication of peripheral sensory end-organs and nerves; thus, the epicritic system of nerves has been developed to amplify and control a more primitive protopathic system. Yet all that we have learned of the evolution of the nervous system encourages us to think that the elaboration and refinement of nervous function has been attained, not by any multiplication of peripheral organs, but by increasing differentiation and integration of function in the central nervous organ. Since its first appearance, the spinal cord has evolved but little, the peripheral nervous system probably even less.

It is therefore improbable that the development of sensory function can have been reached by anatomical additions to the peripheral sensory mechanisms. In his Gifford Lectures ("Man on his Nature," Cambridge University Press, 1940) Sherrington makes a reference germane to this point. "The naive observer," he remarks, "would have expected evolution in its course to have supplied us with more various sense organs for ampler perception of the world. . . . The policy has rather been to bring by the nervous system the so-called 'five' into closer touch with one another. A central clearing house for sense has grown up. . . . Not new senses, but better liaison between old senses is what the developing nervous system has in this respect stood for." (pp. 287-89).

Within the past few years our knowledge of the anatomical basis of cutaneous sensibility has advanced considerably, and Woollard (1940), by the use of a simple direct method of examination of sensory nerve fibres in the skin, has restored structure to its proper place in the study of the sensory nervous system. Electro-physiological methods in the hands of Adrian and others have also taught us much about the nature of the nerve

impulse, and have forced us to abandon the notion of sensory impulses of various specific qualities. The moment seems ripe, therefore, for a general review of our knowledge of the factors underlying cutaneous sensibility.

II.—Head and Rivers' Theory of the Afferent Nervous System and Some of its Corollaries.

In the classic series of studies on the sensory nervous system with which Head and his collaborators have enriched clinical neurology, three of the early papers were devoted to the peripheral nervous system. From their investigations of the sensory changes following upon injuries of various peripheral nerves, and more particularly from the minute study of an area of sensory loss experimentally produced on Head himself by the section of the radial nerve in his left forearm, Head and Rivers came to very striking and definite conclusions as to the constitution of the peripheral nervous system on the afferent side. Expressed at this stage as briefly as possible, their theory is that the cutaneous afferent nervous supply is dual and consists of two anatomically and physiologically distinct systems of receptive end-organs and conducting neurones. One of these, which they call the *protopathic system*, is more primitive both in its origin and in the nature of its activity than the other, or *epicritic system*, which becomes the dominant partner with reactions of considerable refinement. In addition to these two purely cutaneous systems the structures deep to the skin have their own sensory nerve supply. The peripheral afferent nervous system consists, therefore, of three fibre systems. The division of function between them and the relations in which they stand to one another, as described by Head and Rivers, form one of the most complex chapters in the physiology of the nervous system, and one which, if we accept their theory, is of fundamental importance.

In later studies, Head and his co-workers traced the passage of afferent impulses through the spinal cord until they finally reach the highest centres and enter into consciousness to form the basis of sensation. Into each of these studies the theory of the constitution of the peripheral nervous system to which brief reference has been made was woven, and with the publication of the last of these, that on "Sensation and the Cerebral Cortex," took a permanent place in Head's conception of the whole afferent nervous system.

Yet the implications of this initial conception of the peripheral sensory endowment were to be extended still further, for in the course of his

investigation with Riddoch of the reflex phenomena of the divided human spinal cord, Head (H., p. 467) came to the conclusion that the reflex activity of the isolated portion of the cord shows the general features characteristic of the reactions of the protopathic system. The " mass reflex " which they described in spinal man seemed to them to present the counterpart on the motor side of protopathic sensibility. Thus arose the conception of a primitive animal form endowed with an entire nervous system of protopathic quality. Lastly, in his book " Instinct and the Unconscious," Rivers (1920) boldly attempted to construct a biological theory explaining the primitive instincts and the genesis of the psychoneuroses on the analogy of a protopathic nervous system.

Clearly, therefore, the importance of Head's original theory of the sensory nervous system is far-reaching, for it must influence our entire conception of the development, structure and functions of the nervous system. Its foundations must therefore be closely scrutinized. There are several ways in which this task may be approached, but they are not all equally open to us. Thus, the value of the facts of observation recorded by Head and Rivers can be assessed fully only by those who repeat them. This was done by Trotter and Davies (1909, 1913), whose findings and conclusions differed in essential respects from, and are on record for us to compare with, those of Head. However, there are other avenues of approach to this complex problem that do not appear to have been fully explored as yet. Firstly, we may study the theory as formulated by Head and try to determine whether it is the simplest and least speculative generalization of the recorded facts. Secondly, we may examine the final conception of the development and activity of the afferent nervous system proposed, in the light of the general body of physiology and biology. Thirdly, we may take the " protopathic animal " and attempt to determine its possible place, if any, in the evolutionary series.

(i) *The Peripheral Sensory Mechanism.*

According to Head and Rivers, section of a cutaneous nerve results in the production of an area of altered sensibility with a sharply defined border within which the skin is wholly insensitive to cotton-wool touch cf. diagram, p. 71). Situated more or less centrally within this area is a region which is, in addition, totally insensitive to painful and thermal stimuli and is surrounded by an intermediate zone of skin (between it and the margins of the area of tactile anæsthesia) sensitive to painful stimuli (pin-prick) and to extremes of temperature (above 37° C. and

below 26° C.) but anæsthetic to cotton-wool touch. Sensibility to painless and painful deep pressure remains intact throughout the entire area of cutaneous sensory change, and the capacity of localizing the spot pressed remains unimpaired. However, the two points of the compass simultaneously applied to the skin (Weber's test) cannot be discriminated at all within the area of tactile anæsthesia. Further, the sensibility of the intermediate zone is not only diminished in range as compared with normal sensibility, but it is also qualitatively different from that possessed by normal skin. Thus, the prick of a pin is abnormally painful and arouses an almost irresistible desire to withdraw the part pricked. Also, the pain is diffuse, radiates and cannot be accurately localized.

When it begins, regeneration was thought to occur in two stages, widely separated in point of time. The first stage consists in the gradual development within the central area of the mode of sensibility possessed from the outset by the intermediate zone. Thus, painful stimuli and extremes of temperature were perceived through the entire area by the end of seven months from the date of section of the nerve. The qualitative sensory alterations previously noted in the intermediate zone were also present throughout the area; the pain of a prick was intolerable, cold was unduly cold and warmth unusually pleasant. Further, a form of tactile sensibility began to appear. When hair-clad skin within the affected area was stimulated by cotton-wool a diffuse, tingling and referred sensation was perceived. When the skin was shaved this sensory quality disappeared. Head speaks of this as a peculiar form of "hair sensibility" belonging to the protopathic system. A threshold above the normal was observed for all these sensory qualities, and there was radiation and inability to localize stimuli.

According to Head, this range of sensory functions is subserved by a system of punctate end-organs in the skin: pain, heat and cold spots and hairs. Many months after the full establishment of this state of affairs, the second stage of restoration of function begins. The diffuse, radiating and non-localizable quality of sensations disappears, the threshold lowers to normal, the over-response abates and sensibility to cotton-wool touch begins to reappear, and with it the capacity to discriminate two simultaneous contacts. It becomes possible to discriminate thermal stimuli of temperatures less removed from that of the skin than formerly. Finally, all sensations aroused come to bear a close relation to strength of stimulus. To generalize all these phenomena of sensory loss and recovery, Head and

Rivers evolved the hypothesis that the sensory mechanism of the peripheral nerves consists of three anatomically distinct systems of nerve fibres and end-organs.

(*a*) *Deep sensibility*.—This responds to moving stimuli and to painful or painless degrees of pressure. The fibres of this system are distributed with the motor nerves, and are therefore not interfered with by section of a cutaneous nerve. This form of sensibility remains intact when a purely cutaneous nerve is divided.

(*b*) *Protopathic sensibility*.—This is the sensibility of the intermediate zone and of the whole area at the end of the first stage of regeneration. It is also the sensory state of the normal skin covering the glans penis. It responds only to painful cutaneous stimuli and to extremes of heat and cold. It includes also a form of hair sensibility distinct from light touch. It has a high threshold and the sensory response is maximal, ungraded, diffuse and erroneously referred.

(*c*) *Epicritic sensibility*.—This is a sensibility to light touch, to intermediate grades of temperature (between 22° and 40° C.).[1] It includes the capacity to localize single and simultaneous two-point tactile stimuli. It is a low threshold mode of sensibility.

Therefore purely cutaneous sensibility is subserved by two mechanisms, and since in a given nerve the area of epicritic supply is apt to be greater than that of protopathic sensibility, the division of the nerve provides a spatial dissociation of the two modes of sensibility, a narrow zone of pure protopathic sensibility (the "intermediate zone") surrounding the central area of cutaneous anæsthesia. There is also a temporal dissociation, since the protopathic mode is restored earlier than the epicritic (in terms of anatomy, the protopathic fibres regenerate more rapidly than the epicritic), and a stage is reached when the entire area of sensory change is innervated solely by protopathic sensibility. That is to say, the sensory qualities exhibited by the intermediate zone immediately after nerve section are identical with those shown by the entire area at the end of the first (protopathic) stage of regeneration. The later regeneration of epicritic fibres provides a second stage in the restoration of function. Further, the disappearance of the peculiar qualities of protopathic sensibility, namely, maximal ungraded response, diffuseness and absence of localization, when epicritic regeneration is complete, is said to prove that the epicritic system inhibits or dominates the protopathic; a conclusion that allows us further

[1] Head gives varying figures on this point in his different expositions.

to suppose that the protopathic is a primitive mechanism of earlier phylogenetic development than the epicritic system.

It has been mentioned that nothing is directly known of the structures postulated by Head in his hypothesis of a dual sensory mechanism in the skin, and the form assumed by these in his exposition seems to be determined by what Head conceived to be structural necessities of the functions he was investigating. Pain, a purely protopathic mode of sensibility, is subserved by punctate end-organs, the pain spots. Protopathic thermal sensibility is said to be subserved by the "heat" and "cold" spots that earlier investigators had noted, but epicritic heat and cold are believed by Head to be subserved by some non-punctate system of end-organs the morphological characters of which he nowhere discusses. Tactile sensibility (light touch) is subserved by the punctate touch spots belonging entirely to the epicritic system. In hair-clad skin these are grouped round hair bulbs, but in hairless skin—such as the finger tips—they are so closely grouped in the skin that it is difficult to demonstrate their punctate character. In addition to these epicritic touch spots, which Head says are not analogous with pain, heat and cold spots (though how they differ is not stated), there is a peculiar form of protopathic tactile sensibility, called "hair sensibility," which appears to employ the same end-organs as epicritic touch. The qualities of protopathic hair sensibility are its lack of accurate localization and a peculiar tingling quality. How a single type of end-organ can subserve these separate and differing modes of sensibility is not explained. This arrangement is most easily seen in tabular form:

Pain:	Punctate end-organs (pain spots)	protopathic
Thermal Sensibility: Punctate end-organs	{ heat spots / cold spots }	protopathic
Thermal Sensibility: Non-punctate end-apparatus of unspecified nature		epicritic
Touch:	Punctate end-organs (touch spots)	both epicritic and protopathic

That the primary modes of cutaneous sensibility should be regarded as being dealt with by the nervous system in this discrepant manner suggests that the exigencies of hypothesis have borne too hardly upon the facts: an impression that is not lessened when we learn, as will be seen, that when they reach their first synaptic junction in the spinal cord, the qualitatively distinct nerve impulses assumed to be generated in this odd assembly of end-organs lose the specific qualities that it is the latter's prime function to confer upon them. This, summarized, is the theory of

the constitution of the peripheral sensory system formulated by Head and Rivers.

It is now necessary to examine how this anatomical background must influence the manner in which impulses arising in these cutaneous systems are integrated within the central nervous system: a task that involves a consideration of the entire series of studies made by Head and his collaborators on the sensory system.

(ii) *The Integration and Fate of Sensory Impulses in the Central Nervous System.*

Head points out that "between the impact of a physical stimulus on the peripheral end-organs of the nervous system, and the simplest changes it evokes in consciousness, lie the various levels of physiological activity. The diverse effects produced on the living organism by a stimulus are sorted, combined and inhibited in their passage through the central nervous system and the ultimate results finally act upon their appropriate centres. This process of integration takes place apart from any direct participation of consciousness; and, by the time afferent impulses reach one of those centres where they can form the underlying basis of sensation they have been profoundly modified" (H., p. 245).[1] Again, "the stimuli of daily life are not simple, they are extremely complex and give rise to a multitude of diverse impressions. They must be resorted and regrouped; some are facilitated, others repressed before the final sum is presented to consciousness."

To achieve these ends, Head postulates two processes which he names "specific combination" and "selective inhibition," and these it becomes necessary to consider in some detail.

How complex this process of integration must be is evident when we recall that not only has Head postulated a dual peripheral sensory mechanism, but also two separate central sensory mechanisms of distinct phylogenetic rank and physiological function; namely, the optic thalamus and the sensory cerebral cortex. Of these, the thalamus is the older and is normally under the dominance of the cortical sensory mechanism. The thalamic syndrome is regarded by Head as exemplifying the "release" of the primitive and subordinate sensory thalamic mechanism, just as

[1] All references to the papers of Head will be given by page numbers from Head's collected papers published in two volumes under the title of "Studies in Neurology," Oxford Medical Publications, 1920, while reference to Rivers' separate exposition, published under the title of "Instinct and the Unconscious," Cambridge University Press, 1920, will be referred to also by page numbers and the initial "R."

protopathic sensibility represents the comparable release of a primitive peripheral mechanism.

We are naturally concerned to ask as to the relations of the two peripheral with the two central sensory mechanisms, and we find, in fact, that this relationship is nowhere clearly formulated and is indeed the subject of great conflict of statement. Rivers (R., pp. 28 and 48) maintains that protopathic sensibility is inhibited at the periphery, but that the thalamus is the central representative of protopathic sensibility. Head offers two quite different accounts. According to him, the special qualities of protopathic and epicritic sensibility cease to exist when the impulses subserving them enter the cord and pass into the second level neurones. Thus, once the first synaptic junction is passed "it is no longer a question of protopathic, epicritic and deep sensibility" (H., p. 335), for "the characteristic features of protopathic and epicritic sensibility disappear" at this junction (H., p. 651). Yet he adds that protopathic impulses are checked within the central nervous system by coincident epicritic impulses, this check taking place at a level higher than the end station of sensory impulses in the thalamus (H., p. 653).

Here we have four different accounts of a single process, and the reader begins to become aware of the insuperable difficulties introduced into Head's theory by the postulation of a dual peripheral sensory mechanism. Yet, somehow and somewhere within the central nervous system the epicritic system has to achieve its dominance over the protopathic. As to the "how" of this dominance Head, as we have seen, believes it to be achieved by specific combination and selective inhibition, but as to the "where" no clear and consistent view is to be found in the series of papers in which the theory is expounded.

In considering the process of specific combination a difficulty meets us at the beginning, for it is based upon a conception of the nerve impulse that later work has shown to be untenable. The complex stimuli that play upon the surface of the organism give rise to impulses in the end-organs of the protopathic, epicritic and deep systems, "each impulse," according to Head, "being stamped with the characteristics peculiar to the end-organ in which it has arisen" (H., p. 644). In particular, the protopathic impulse is said to be "heavily charged with feeling tone." Yet we now know that the individual sensory nerve impulse shows no evidence of any specific qualities, and could not in any case possess the psychological quality of "feeling tone."

Nevertheless, let us examine what is actually postulated of specific com-

bination. By it all sensory impulses reaching the spinal cord are sorted into new pathways, each of which subserves a special mode of sensibility: tactile, thermal, painful or postural. Thus, "the afferent consequences of all stimuli capable of evoking a sensation of heat, whether of epicritic or of protopathic origin, are gathered together into special secondary tracts. The entrance to these is guarded by specific 'intramedullary receptors' which, like resonators, are attuned to pick up one particular quality of impulse" (H., p. 651). Further, "when an impulse which has originated in the effective stimulation of a heat spot belonging to the protopathic system, reaches an intramedullary receptor of the secondary system set aside for impulses of heat, it starts a specific impulse. But the same receptor reacts to the epicritic impulses which are started by stimulation of the skin with temperatures between 32° and 40° C." (H., p. 404). Thus, it is inevitable that the specific qualities attributed to protopathic and epicritic impulses should disappear when a common secondary pathway is entered. It is not easy to see what role is now left for selective inhibition, or what can be the nature, or what the necessity, of a process by which epicritic sensibility achieves its dominance over a special variety of protopathic impulse that, as it were, loses its characteristics spontaneously when it enters the secondary pathway. Despite this, it is clear from other expositions of the theory that the special qualities of the protopathic impulse are required to survive until the end station in the thalamus has been passed by the ascending impulses.

Anatomically, the rearrangement is said to be as follows: Impulses subserving thermal and painful modes of sensibility enter the secondary path upon their entry into the cord; this path decussates and turns upwards in the crossed lateral column (lateral spino-thalamic tract). Impulses subserving postural sensibility and tactile sensibility (including two-point discrimination) do not enter the secondary path at once, but turn upwards, still in the primary neurone, in the posterior column of the side of entry. They meet their synaptic junction at the posterior column nuclei of the medulla and, entering the secondary path which decussates at once, undergo a regrouping in which postural impulses, tactile impulses, and separate impulses subserving two-point discrimination all travel in distinct secondary paths. But tactile impulses exist of another order. These, subserving the sense of touch and localization, are rapidly filtered off into a secondary path which decussates and turns upwards in the crossed half of the cord in the ventral spino-thalamic tract.

Specific combination is thus completed, and all modes of sensibility

are now travelling in secondary pathways grouped as follows: (i) postural; (ii) thermal; (iii) painful; (iv) impulses subserving the sense of touch; (v) impulses subserving single spot localization; (vi) impulses subserving two-point discrimination. It should be noted that the two last categories do not subserve the appreciation of touch, but only the qualities named.

Consideration reveals that this remarkable process, though avowedly only an anatomical rearrangement, has effected (or is presumed to have effected) qualitative changes in sensory impulses, and has abstracted from tactile impulses two of the qualities of normal tactile sensibility. Thus, the deep afferent end-organs normally respond to deep pressure and possess the capacity of localizing a single pressure stimulus, but they lack the capacity, according to Head, of two-point discrimination (Weber's compass test). Tactile end-organs subserve light touch, localization and two-point discrimination. Yet once the impulses arising in the two sets of end-organs concerned enter the secondary pathway "all distinction is lost between those arising in different peripheral systems. The lightest touch and the heaviest pressure, short of discomfort, form the two ends of a graduated tactile scale" (H., p. 655). That is to say, a qualitative identity has been conferred upon sensory impulses that prior to spatial regrouping were not identical in character. Even more profound is the effect of specific combination upon tactile impulses, for once the secondary path is entered, localization and two-point discrimination each has its own anatomical pathway distinct from that subserving the appreciation of touch.

Now, as a mental act on the observer's part it is possible to abstract separate qualities from a single natural function. Thus, we can *think* of tactile sensibility, localization and two-point discrimination as abstractions and separately, but they cannot exist apart in nature. There is no such *thing* as localization or discrimination, there are only things localized or discriminated, and we cannot conceive of an impulse that allows us to localize or to separate without making us aware of the things localized or separated. This conception of sensory functions clearly embodies a confusion of thoughts with things, and even though clinical examination should in a given case of sensory alteration reveal apparent dissociations of these three aspects of tactile sensibility, we cannot account for such dissociations in this way. In short, the notion of pathways for localization or for discrimination are in the same category as that of pathways for truth or beauty, and are but figments of the observer's mind. Two-point discrimination presupposes the simultaneous stimulation of spatially

separated end-organs in the skin and subcutaneous tissues. From each end-organ thus excited, volleys of separate impulses must travel by different nerve fibres to the highest cortical centres, there to form the basis of a discriminating judgment. That a multiplicity of end-organs probably underlie two-point discrimination is to be inferred from Trotter's observation that excitation of cutaneous tactile end-organs alone is inadequate to secure accurate two-point discrimination: deep end-organs must also be stimulated. While, as quoted by Trotter, Spearman found that this discrimination waned in acuity in the presence of muscular fatigue. Therefore, cutaneous, subcutaneous and muscular afferents probably all combine to provide the sensory material out of which discrimination is achieved. In other words, it is a judgment and not a mode of sensibility: a judgment made as a result of integration in the only place where such integration can occur, namely, in the cerebral cortex. Head (H., pp. 392-5) provides evidence of this order, when he finds that posterior column lesions impair two-point discrimination and postural sensibility together, while Holmes (1927) has pointed out that disturbance of discrimination of one from two-point stimuli is frequently the most striking effect of a lesion involving the sensory cerebral cortex: another indication of the cortical seat of the physiological processes involved.

As for localization, it does not appear from Head's clinical records that there is any necessity or justification for postulating a divorce of contact sensibility from localization. The cases he believes to reveal this separation do not unequivocally do so. These cases consist of (i) one of glioma involving the mid-brain where the most that could be stated was that the disturbance of localization was "out of proportion to the disturbance of tactile sensibility," and (ii) of twenty-four cases of the thalamic syndrome in which the majority showed defects in tactile sensibility, but only twelve cases showed comparable defects in localization. In other words, tactile sensibility was found disturbed more frequently than localization, but it is not recorded that the latter was defective when the former was normal. In short, a significant dissociation of localization from tactile sensibility appears not to have been noted.

In conclusion, then, as elaborated by Head, specific combination is an incredible function. The role and nature of selective inhibition are equally difficult to understand. The protopathic thermal impulse with its heavy charge of "feeling tone," its radiation and erroneous localization, having reached the thalamus has to be appropriately modified by the coincident epicritic thermal impulse. The aspect of thermal sensibility subserved by

the former is believed to reach consciousness in the thalamus, while epicritic thermal sensibility is a function of the sensory cerebral cortex. How does the latter prevent the undesirable qualities of the former reaching consciousness? There seems no alternative but to suppose that the cortical control of thalamic sensibility *is* the epicritic control of protopathic sensibility. Yet, clearly, this it not Head's view, and if it were so the sensory features of the thalamic syndrome should be those of protopathic sensibility as revealed in the intermediate zone after peripheral nerve section. Yet, again, thalamic sensibility is not identical with protopathic sensibility, and it is not possible to discover in what selective inhibition really consists and how it is achieved. Rivers, conscious of the difficulty, supposes that thalamic sensibility differs from protopathic, because the characteristic features of the latter are inhibited at the periphery. Yet this notion runs counter to our knowledge that in the cerebrospinal nervous system, inhibition is a central and not a peripheral function. In short, no provision is made in Head's hypothesis for the attainment of epicritic dominance, and the reader arrives at the final stage of this hypothesis with a profound sense of confusion.

In short, as we trace this hypothesis from its beginnings to its ending, we find it increasingly and, at last, fatally embarrassed by the necessity of weaving into its fabric the dual peripheral sensory mechanism with the hypothecation of which it began. Speculative anatomical structures, different for each mode of sensibility, and physiological processes, inconceivable in nature and often mutually exclusive, have to be assumed from stage to stage in the endeavour to harmonize the initial with the final stages of the hypothesis, so that the complete form taken by this wholly lacks coherent meaning. This is not to say that the impressive body of observations upon the sensory changes that ensue upon lesions of the spinal cord, brain-stem and cerebral hemispheres that we owe to Head is not a great achievement and a notable contribution to neurology; it is simply to submit that Head's generalizations from these observations are unsatisfactory and do not provide a theory of the afferent nervous system that we can accept. Yet despite the fallacies that we may think we detect in the interpretations advanced by Head, the crux of any criticism of his work must lie in the detection of errors of observation. In respect of the sensory changes ensuing upon lesions of peripheral sensory nerves, it has to be admitted that no subsequent observer has confirmed Head's findings in certain essential details and that no convincing evidence of a dual peripheral sensory mechanism can be found. His theory of the afferent nervous

system must, therefore, be rejected on factual as well as on theoretical grounds.

(iii) *Dissolution of Function in Disease and Injury of the Nervous System : Jackson's Hypothesis and Head's Interpretation of it.*

It is the fascination of Head's theory that it constantly brings the student up against fundamental general principles in biology and neurophysiology. In this attempt to generalize from his observations of sensory and motor disorders, we meet an important general principle.

To understand how Head and his collaborators have reached their significant conclusions, it is necessary to consider the method they adopted in their approach to the problems of cutaneous sensation. Briefly, all the work on the afferent nervous system we have reviewed is based upon the study of residual sensibility. In the case of a nervous lesion affecting sensation we have to study not only the degree and nature of sensory loss ensuing, but also the nature of such sensation as remains. Now, Head and Rivers in investigating the area of altered sensibility resulting from the nerve section on Head's forearm, believed that they were able to distinguish by the method of residual sensibility a dissociation of normal sensibility into deep and cutaneous systems. Further, the study of the intermediate zone of the area of altered cutaneous sensibility, and of the alleged two-stage regeneration, led them to conclude that there were two systems of cutaneous innervation, protopathic and epicritic. Similarly, in tracing the path of sensory impulses from their point of entry into the central nervous system to the highest centres, the same method of residual sensibility was employed to discover the specific combination and the selective inhibition of sensory impulses, in short, their integration before they come to appear in consciousness as sensations.

The entire nervous system reacts to injury of one of its component parts, and the mutilated residual innervation remaining is itself probably composed of several factors and is capable of resolution into elementary components. What is the significance of this residual innervation? In considering this question we are at once reminded of Hughlings Jackson's teaching upon the dual nature of nervous symptomatology and upon the mode of dissolution of function in the nervous system. Upon the former point the principle he enunciated was admirably summarized by Broadbent as follows: The functions of a centre in which a lesion has occurred are suspended, and corresponding symptoms may be called negative. These are, however, not the only symptoms; others, usually more obtrusive, and

often infinitely more important, are produced by the activities of other centres, either (i) unbalanced in consequence of the absence of normally opposing activities; or, (ii) liberated from the control of higher level centres; or, (iii) intensified by attempts to compensate for the missing function. Nervous disease therefore effects a reversal of evolution. "Dissolution is a process of taking to pieces in the order from the least organized, the most complex and the most voluntary towards the most organized, the most simple and the most automatic," and again, "dissolution being partial, the condition in every case of it is duplex. The symptomatology of nervous diseases is a double condition; there is a negative and there is a positive element in every case. Evolution not being entirely reversed, some level of evolution is left." Hence the statement "to undergo dissolution" is rigidly the equivalent of the statement "to be reduced to a lower level of evolution." (Selected Writings of John Hughlings Jackson, 1932, vol. 2, p. 46). It is to be noted, however, that Jackson nowhere suggests that the lower planes of evolution exposed by disease or injury necessarily represent physiological states that in earlier stages of phylogenetic evolution were the normal endowments of primitive nervous systems, nor did he suggest that dissolution of function was associated with the release of primitive anatomical systems to resume their original activities in their pristine form.

That Jackson's generalizations have been, and will continue to be, of the greatest importance to neurological thought will not be disputed, and his conception of the release mechanism is perhaps one of his most valuable contributions. Yet it may be questioned whether sometimes too much has not been demanded of it. As commonly applied, there is no place for qualitative changes in function apart from simple increase or defect. There may well be perversions of function not thus easily to be generalized. In short, generalizations are dangerous in proportion to their value unless they are constantly correlated with the facts of observation. As Trotter (1913) has observed: "In dealing with theoretical considerations concerned with the physiology of the nervous system, one is exceptionally liable to be misled by preconceived or introspectively evolved notions as to how sensory and perceptive processes may be supposed to act. Symmetry and the desire for classification are apt to be mistaken for physiological principles and we tend to drift into the error of supposing that conceptions which are clear cut, easily comprehensible and 'reasonable' acquire by that very fact an increased probability of being accurate expositions of the physiological processes they profess to explain. This has been repeatedly demonstrated in the history of neurology."

With these considerations in mind we return to Head's view that protopathic sensibility is " the level of evolution left " when a higher level epicritic system is out of action. It thus represents a primitive form of sensibility unmasked after its continuous suppression for countless ages in phylogenetic history. This being so, are we to assume that it is now revealed precisely as it originally was, or has its long suppression so modified it that what now appears resembles nothing that previously existed? If such a modification has taken place, how shall we determine its degree and kind? How can we even know that it has taken place? In truth we cannot know any of these things. On the other hand, if we are to assume that it now approximates in characters to a normal primitive sensory function, it should provide valuable information as to the mode of evolution of function in the nervous system.

Rivers (R., pp. 22-33) states that protopathic sensibility—and the mass reflex—do represent the reappearance of once normal forms of primitive nervous activity. Head's views are exemplified by the following quotations: " The final act of sensation can be decomposed by changing its physiological components. The form assumed by such dissociation may resemble nothing that has previously existed in the phylogenetic history of man; or the change may approximate to the character of some more primitive activity. This is the case with high grade protopathic sensibility and with sensations from the glans penis " (H., p. 8). Against this, we read (H., p. 743): " Removal of epicritic sensibility exposes the activity of the protopathic system in its full nakedness. In the same way, when removal of the influence of the cortex cerebri sets free the optic thalamus from control, sensation assumes an overwhelmingly ' thalamic ' character. In each case a more primitive organization is kept under control by the activity of a higher afferent system. But removal of the dominant mechanism does not reveal the functions of the phylogenetically older organs in all their primitive simplicity. A lesion which sets free the human thalamus produces a highly specialized series of phenomena, which have never existed in this form in phylogenetic history." Again (H., p. 745): " many lower activities are retained in a controlled form and are not abolished in the course of evolution because they may be required at some time or another for their primitive purpose." But although thus controlled the primitive mechanism " must remain in full activity, ready to play its part, should occasion arise, in the defence of the body against noxious influences."

Surely, if these primitive functions may have to resume their original

activity fully, as Head supposes, they must retain their original characters and not reappear in a form "which has never existed in phylogenetic history." A comparable conflict of statement informs Head's elucidations of the "mass reflex," for while this is not to be regarded as "reproducing an ancient mechanism in its primitive form," it is said to "reappear in its primitive form" immediately the spinal cord is transected.

Apart altogether from these inconsistencies, we may well ask whether we can accept the notion of an inhibition that has persisted uninterrupted throughout the countless ages of phylogenetic history, and yet remains an immediately reversible phenomenon.

Nevertheless, it is clear that Head's theory of the afferent nervous system does in effect require that both protopathic and thalamic sensibility, as well as the mass reflex, should all be regarded as unmasked forms of primitive nervous activity, not essentially changed by their age-old suppression.

No hypothesis largely dependent upon phylogenetic considerations can ever be capable of scientific proof, yet it may well have the compensating attraction of being equally incapable of disproof, and there are always some who are ready to accept an hypothesis upon these equivocal terms. This readiness has been indicted by Karl Pearson in his "Grammar of Science" thus: "It is easy to replace ignorance by hypothesis, and because only the attainment of real knowledge can in many cases demonstrate the falseness of hypothesis, it has come about that many worthy and otherwise excellent persons assert an hypothesis to be true because science has not yet by positive knowledge demonstrated its falsehood."

(iv) *The Phylogenetic Significance of a Protopathic Nervous System.*

Having seen the necessarily speculative nature of hypotheses that invoke phylogenetic factors, we may consider briefly the hypothetical protopathic animal. On the sensory side it possesses a sensibility that presents "none of those characters of sensation by which we recognize the nature of the (stimulating) object, no power of distinguishing difference in intensity, nor of telling with exactness the spot stimulated" (R., p. 23). "It would have no necessity for the discrimination which would enable the exact perception of the nature of the object" (R., p. 30). In fact, its sensibility possesses "elements of vagueness and confusion wholly incompatible with the exact power of localization." On the motor side the animal is not less handicapped, for in the mass reflex, which exemplifies its characteristic mode of movement, "the situation of the stimulus does not determine the dis-

tribution of the response." The mass reflex consists of powerful bilateral flexion of the limbs, contraction of the abdominal muscles, evacuation of the bladder and an outburst of sweating. This response is not adapted to the strength or site of stimulation, but is maximal and unvarying, yet Head speaks of it as "an excellent answer to noxious stimuli in the lower animal"; able to respond only by a mass movement, the animal is "fixed in a position unfavourable to flight and crawls into a hole to die or recover" (H., p. 753).

Such a creature, even if it could take the steps necessary to propagate its bewildered kind, which appears doubtful, could have no survival value, for on receipt of a stimulus which it could not localize, from a stimulating agent whose nature it had no means of discovering, it could respond only by curling up and micturating. Yet this is the animal that Head and Rivers present to us as our common ancestor.

It is not necessary to pursue this line of thought further, or to consider the theory of instincts and of the genesis of the psychoneuroses elaborated by Rivers upon a foundation so fantastic.[1]

Perhaps a more conclusive and less dialectical criticism of the protopathic nervous system may be found when we come to consider the reactions of the simplest forms of nervous system known to biologists. Parker has described such a one in the polyp, Corymorpha. Describing this creature, Parker (1919) says: "If a faradic stimulus is applied to one side of the stalk next the hydranth or the base, the stalk simply shortens as a whole. If, however, the stimulus is applied to one side of the stalk nearer the middle of its length, the stalk bends to that side and usually presses the hydranth with great accuracy against the spot. This response is not only appropriate for the particular side stimulated, but also in most cases for the given level of the stimulated spot on that side. . . . The success of this form of protective response naturally depended upon the accuracy of the localization." Here, therefore, the most primitive of animals appears already to have sensation of "epicritic" quality. Nowhere in nature, in fact, do we find a nervous system in any way comparable with the "protopathic" system of Head and Rivers. As Sherrington has pointed out, a simple act of co-ordination may be as perfect as a highly complex one. The prime function of the nervous system is integration, as we have learned from Sherrington, and the terms "primitive" and "crude" so repeatedly employed by Head and by Rivers

[1] This theory has been discussed elsewhere by the present writer, cf. *Med. Sc.*, 1922, 6, 216.

cannot properly be applied to even its simplest activities; they are, in fact, terms that create an impression in the reader's mind, but convey no information. At every stage of its evolution, as exemplified in the extant animal kingdom, the nervous system is seen to be an instrument of precision. It is its very nature and purpose to be such, and the conception of a protopathic nervous system as outlined by Head and Rivers runs directly counter to all we know of biological processes as these are to be seen in the evolution and activity of the nervous system.

III.—The Observations of Trotter and Davies on Cutaneous Sensibility.

These were more exhaustive than those of Head and Rivers in that no less than seven cutaneous nerves were divided at intervals of time in two subjects. It was thus possible to make adequate immediate comparisons of the consequences of nerve section at all periods after the division. There was no necessity to rely, as in Head's case, upon the sensations of a single observer, or upon his memory in comparing the immediate sensory results of nerve section with those of the stages of regeneration. The importance of this enhanced opportunity for the control of what are peculiarly difficult observations and unfamiliar subjective judgments is manifest. These observations were published in two papers: "Experimental Studies on the Innervation of the Skin (*J. Physiol.*, 1909, **38**, 134) and "The Peculiarities of Sensibility found in Cutaneous Areas supplied by Regenerating Nerves" (*J. für Psychol. u. Neurol.*, 1913, **20**, 102). It is unfortunate that the latter paper has remained so unfamiliar to English-speaking neurologists, for it is an essential complement to the former.

In so far as Trotter employed the technique of investigation used by Head, his observations seem at first not to present any essential difference from the latter's, but differences there clearly are and they prove to be of fundamental importance when conclusions come to be drawn from them. With the employment of additional methods, it appeared that changes in cutaneous sensibility not discoverable by Head's methods were present, and thus a still wider departure from his generalizations became necessary. In brief, Trotter was unable to confirm Head's description of the sensory qualities of the intermediate zone; nor the qualitative identity of this with the state of the affected area at the end of Head's first stage of regeneration; nor, in conclusion, did Trotter find that regeneration takes place in two stages.

A preliminary idea of the discrepancies between the observations of

the two may be gained from the facts concerning thermal sensibility in the intermediate zone of Head. Head does not state whether the thermal stimuli in the intermediate zone give rise to thermal sensations of normal intensity: as they should do were these sensations a function of an intact protopathic thermal system—as by definition they are. Trotter finds that this so-called thermal sensibility to extremes of temperature is in fact a hypoæsthesia: stimuli which on normally innervated skin give a sensation of "hot" or "cold," giving sensations of "warm" and "cool" only. This finding is incompatible with Head's hypothesis. Further discrepancies will be referred to in due course.

In a preliminary discussion, Trotter points out that although graduated punctate stimuli may be necessary in the investigation of sensory function, yet such stimuli are not physiological in the sense that the surface of the normal organism under normal conditions does not receive single stimuli of this nature, but more widely distributed and qualitatively multiple stimulations, often affecting simultaneously end-organs of diverse kinds. In accordance with this principle it is found that the most accurate way of delimiting the external margins of an area of altered skin sensibility after cutaneous nerve section is to let the subject stroke the skin with his own finger. In this way a larger area of change is found than the most carefully graded punctate stimuli (tactile stimuli) suffice to determine. Stroking is at once a more physiological and a more delicate mode of stimulus than a von Frey hair.

(i) *The Immediate Consequences of Nerve Section.*

Briefly stated, the following are, according to Trotter, the immediate consequences to cutaneous sensibility of the section of a cutaneous nerve. The area of altered sensation consists of an outer zone of partial, and a central area of total cutaneous sensory loss. The outer zone is delimited most accurately by the stroking method already described. No other method gives so precise a record, or one more constant on repeated examination. Within the margin thus detected, and as stimulation approaches the central area there is found a progressively deepening hypoæsthesia to *all* modes of cutaneous sensibility. The findings may be further particularized: *The hypoæsthetic zone:* Externally this is an area of qualitative change only. Von Frey hairs may give no clear indication of the peripheral limits of the area, but to stroking the skin feels smoother, and tickle, when it is elicited, less intense. Within this region, as the observer passes from periphery to central anæsthetic area, a margin is

reached within which the skin feels subjectively numb and cotton-wool touch, or light strokes with a camel hair brush elicit no tactile sensation whatever. In this zone, the threshold of tactile sensibility to von Frey's graduated hairs rises, but a threshold can be obtained and there is hypoæsthetic tactile sensibility. Finally, as the central area is approached this threshold rises rapidly until the characteristic sense of a touch is lost as this area is reached.

Also within the surrounding hypoæsthetic zone, the threshold of two-point discrimination rises rapidly, but a threshold is always obtainable even in the central anæsthetic area as long as deep pressure sense remains. Trotter finds, also, that contact with a light hair, insufficient to stimulate deep pressure end-organs, does not give precise two-point discriminatory capacity. This is yielded only by combined stimulation of tactile and of deep pressure end-organs.

Another point of importance arises here. Head, in testing tactile cutaneous sensibility, used a fixed-stimulus method: namely, a wisp of cotton-wool, believing that stronger stimuli excited the end-organs of the deep afferent system and not the cutaneous tactile end-organs (touch spots). As a result of this, all grades of tactile sensibility of higher threshold than that of cotton-wool passed undetected by Head. Trotter maintains that cutaneous "touch" is introspectively a distinct mode of sensation, easily differentiated by the subject from the sensations aroused by "pressure" acting on subcutaneous end-organs, and thus he felt himself free to use graduated punctate stimuli (von Frey's hairs) believing that sensations of pressure could be readily differentiated from those of true touch. Acting on this basis, Trotter finds that the hypoæsthetic zone possesses true tactile sensibility.

In respect of thermal sensibility in the hypoæsthetic zone, Trotter draws attention to a point of fundamental importance nowhere recognized by Head. He finds that normally innervated skin yields no response to temperatures within 5° C. of the skin temperature. There is thus an indifferent range of 5° C. on each side of this temperature: that is, a total indifferent range amounting to some 10° C. Thermal hypoæsthesia is expressed in two ways: (i) by a widening of the indifferent range to about 10° C. on each side of the skin temperature: that is, an indifferent range extending over from 15° to 20° C. of the thermometric scale, and by (ii) the diminished intensity of the thermal sensations appreciated outside this indifferent range. What is hot on normal skin is only warm in the hypoæsthetic zone, and what is cold on normally innervated skin is, in the

hypoæsthetic zone, only cool. This significant finding may be expressed in tabular form. The cross-hatched area is the indifferent zone.

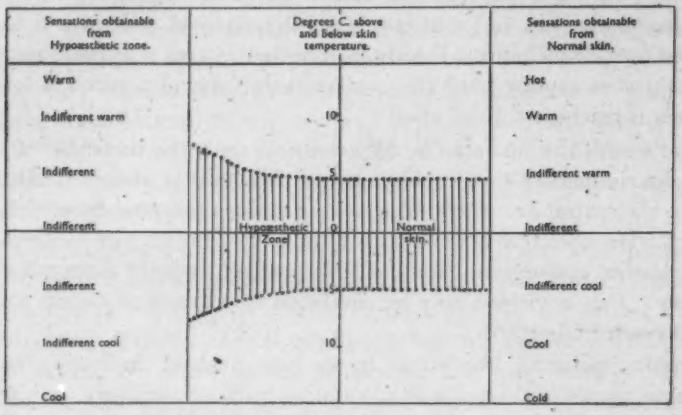

FIG. 1.

Trotter believes that the sensations hot and cold are a combination of warm plus pain and cool plus pain, and points out that at both ends of the thermal scale when supramaximal stimuli are used the sensation felt is pure pain.

In respect of painful sensibility in the hypoæsthetic zone, Trotter finds a comparable state of affairs, that is, a deepening hypoæsthesia as the central area is approached. The defect in sensibility is precisely similar to that for touch, heat and cold.

The hyperalgesia so stressed by Head in his intermediate zone is not constantly present. Immediately following nerve section there is a transitory hyperalgesia for some hours, then a period of about ten days in which no hyperalgesia whatever is present, and then a period of secondary hyperalgesia persisting for some six weeks. This then ceases entirely and for the two or three weeks that yet remain before the first indications of regeneration appear there is no trace of hyperalgesia. When present, this secondary hyperalgesia differs from that described by Head, in that it is very patchy in distribution and does not remain confined to the hypoæsthetic zone, nor fill the whole of this, but seems to be distributed over underlying subcutaneous veins. Trotter believes it to be an adventitious phenomenon and not an essential sensory result of nerve section. He points out that it does not follow the blocking of a cutaneous nerve by

novocain, and also that it differs widely in quality and distribution from the intensification of painful and cold sensations characteristic of the phase of restoration of sensory function.

In short, Trotter finds a central anæsthetic area in which the margins of total thermal, painful and tactile sensibility correspond approximately, but not precisely. Surrounding it is a zone of hypoæsthesia, wider than Head's intermediate zone, and characterized by hypoæsthesia progressively deepening from without inwards to all modes of cutaneous

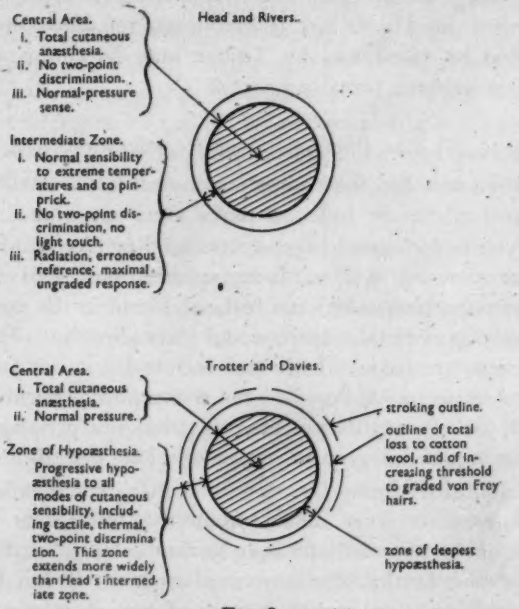
Central Area.
i. Total cutaneous anæsthesia.
ii. No two-point discrimination.
iii. Normal-pressure sense.
Intermediate Zone.
i. Normal sensibility to extreme temperatures and to pin-prick.
ii. No two-point discrimination, no light touch.
iii. Radiation, erroneous reference, maximal ungraded response.
Head and Rivers.
Central Area.
i. Total cutaneous anæsthesia.
ii. Normal pressure.
Zone of Hypoæsthesia.
Progressive hypoæsthesia to all modes of cutaneous sensibility, including tactile, thermal, two-point discrimination. This zone extends more widely than Head's intermediate zone.
Trotter and Davies.
stroking outline.
outline of total loss to cotton wool, and of increasing threshold to graded von Frey hairs.
zone of deepest hypoæsthesia.

FIG. 2.

sensibility. This hypoæsthesia differs in its expression according to the mode of sensibility under examination. Thus, in respect of thermal sensibility it is found that the normal indifferent zone of some 5° C. on each side of the skin temperature is widened to 10° C., and that outside this zone there is thermal sensibility, not of normal, but of diminished intensity. In respect of tactile sensibility, the threshold of stimulation—as measured by von Frey hairs—rises progressively, but once elicited the sensation of light touch is an unvarying one. Two-point discrimination undergoes the same progressive diminution as the central area is approached that is

shown by other modes of sensibility. Trotter does not therefore find a specific loss of tactile sensibility nor of two-point discrimination in his intermediate hypoæsthetic zone. With regard to pressure sensation, he believes that this is mainly subserved by end-organs deeper than those which subserve touch, and probably subcutaneous, but he believes that true pressure sensations may be aroused in the skin. Wherever the points of the compass (Weber's test) could be felt by pressure on the skin, some threshold was to be found. Painful sensibility also undergoes a deepening hypoæsthesia and does not show the characteristic and persistent hyperalgesia described by Head, nor is erroneous reference present. The results obtained by Head and by Trotter may be compared and contrasted, in diagrammatic form in figure 2.

(ii) *The Phenomena of Regeneration.*

Between the tenth and fourteenth weeks after nerve section the initial signs of returning sensory function make their appearance. They are (i) the progressive and simultaneous return of tactile, painful and cold sensations, the return of true heat being apparently delayed; (ii) the development of two new phenomena not hitherto found in the area of sensory change; namely, peripheral reference and intensification. The returning sensory functions are hypoæsthetic and full acuity is not attained for a further period of weeks. Even when the restoration of normal acuity has been reached, the two qualities of intensification and peripheral reference may persist in modified degree for indefinitely long periods.

The first sign of returning function in Trotter's seven experiments was *peripheral reference.* This differs from the diffuseness of response characteristic of the hypoæsthetic zone in the period immediately following nerve section, in that the sensation experienced can be minutely localized towards the distal end of the area of sensory change. It involves tactile, painful and cold stimuli, those of heat less definitely. In respect of touch the sensation actually experienced is almost identical with that evoked by light touch on normal skin, though the threshold of stimulation is higher and when many end-organs are simultaneously excited the resulting sensation has the tingling quality of a mild faradic current. The stimulation of a cold spot gives striking peripheral reference, and painful sensations are also referred. At a later stage in the regeneration process a local reference to the spot actually stimulated may be added to the peripheral reference, and subsequently, this local reference tends to increase in intensity as the peripheral reference wanes.

Closely associated with this phenomenon is that of *intensification*. This imparts an abnormally vivid quality to sensations, even though the threshold may be abnormally high: that is, intensification and hypoæsthesia may co-exist, but it tends to persist after a normal threshold has been reached, and may indeed be still present years after this has happened. It is most marked in the case of cold, least in that of true heat.

A third new phenomenon is that of *increased excitability of the regenerating nerve trunk*. The regenerating nerve trunk is found to be abnormally sensitive to stimulation, and to yield the specific sensations of touch, pain, cold and—less distinctly—of heat, when the appropriate stimuli are applied to the skin overlying it. The sensations thus evoked are referred to the nerve's area of distribution and show intensification and peripheral reference. This quality of excitability is known to obtain in the case of normal cutaneous nerves, though in a very much less marked degree than that exhibited by the regenerating portion of the divided nerve.

In considering the significance of the phenomena of intensification and peripheral reference, Trotter points out that they have no counterpart in the sensory state of the hypoæsthetic zone immediately after section and prior to the onset of regeneration. He believes that peripheral reference is due to nerve trunk stimulation and that this is incapable of yielding a local sensation, the provision of "local sign" being probably a function of the end-organ. The later appearance of local sensation is attributed to the re-establishment of connection between the end-organ and the growing nerve fibre.

Since both intensification and peripheral reference may persist after normal sensory acuity has returned, Trotter maintains that the notion of epicritic inhibition of these qualities is untenable, and that both are the product and result of damage to nervous tissue and of the resulting reaction between this and the surrounding somatic tissues.

Head lays great emphasis upon the supposed existence in the skin of the glans penis of a mode of sensibility purely protopathic in range and quality, and of an area in his own forearm possessed of exclusively epicritic sensibility. These findings he regards as confirming his hypothesis, but Trotter has little difficulty in showing that neither of these skin areas does in fact fulfil the requirements of the hypothesis, and neither allows the deductions Head has drawn.

In conclusion, it is clear that in respect both of the immediate results of nerve section and of the successive sensory states observed during the

process of restoration of function, there are numerous discrepancies between the findings of Head and those of Trotter, and the essential facts relied upon by the former to prove the existence of a duel peripheral sensory mechanism, protopathic and epicritic, are not confirmed by Trotter. It is in generalizing the phenomena of sensibility to pain that the widest differences of view between Head and Trotter are to be found. For the former, pain is a purely protopathic mode of sensibility, of high threshold and non-localizable. Intensification and radiation of pain sensations are for Head essential features of this mode of sensibility, inhibited under normal conditions by the coincident activity of an epicritic system of nerves and end-organs. Throughout Head's numerous expositions, he repeatedly emphasizes the high threshold quality of painful sensibility, as for example "pain is always a high threshold sensation as shown by the fact that it is not evoked by punctiform stimuli until the pressure exceeds 70 grm/mm^2" (H., p. 319). It is to be recalled, also, that protopathic sensibility is regarded by Head as the sole normal sensory endowment of an earlier stage in phylogenetic history of a primitive animal form.

Biologically considered, it seems improbable that a high threshold form of sensibility can ever have been normal at any stage in evolutionary development, for it would be a quality adverse to the evolutionary process, but we do not need to invoke speculative factors of this order to see the fallacy of the conception of high threshold. By what standard is its height measured? Has this standard any biological meaning? Pain, as Trotter points out (1913, p. 138-39), has as its essential function the signalling of potential injury rather than the notification of actual damage, and pain can be elicited by stimuli below the level of intensity at which injury to the tissues is produced. In other words, the threshold for pain is below the level at which damage can be inflicted on the tissues. That it needs a von Frey hair of 7 grm./mm.^{2} to elicit it, is a fact of no physiological meaning, and not one by which we can conclude that pain is a high threshold form of sensibility. Pain serves a specific purpose for the organism; for the fulfilment of this it has a threshold appropriate to this purpose, and not high judged by standards relevant to the needs of the organism. In the electrophysiological studies of pain sensibility that we shall later consider, we find implicit in many papers the same conception of pain as a high threshold form of sensibility: either because pain fibres in nerve trunks are relatively inexcitable to electrical stimuli, or because the pain spots in the skin seem to yield on minimal stimulation a sensa-

tion of touch and only a brief sequence of nerve impulses; a greater intensity of stimulus being necessary to evoke pain and to set up the long lasting sequences of nerve impulses characteristic of pain sensations. But here also the standards of electrical or mass measurement invoked in support of this notion have no biological import. Grams and millivolts as such mean nothing to the organism. The threshold of sensibility to pain can be judged only in the light of the function pain serves in the life of the organism. So judged it is not a high threshold form of sensibility, as Trotter points out.

Conversely, to speak of tactile sensibility as of low threshold, while it is accurate in terms of gram-millimetres square of pressure from a von Frey hair, is to ignore the fact that the threshold is that appropriate to the purpose tactile sensibility serves in the organism: that of underlying the discrimination of spatial relationships. In other words, each mode has the threshold appropriate to its function and to contrast them as "high" and "low" respectively is not to draw a biological distinction but to contrast tactile and painful sensibility in terms of physiologically irrelevant and conventional symbols.

The matter may be further considered. While tactile and thermal end-organs respond only to specific modes of stimulus, the pain endings are found to respond to a wide range of stimuli, and thus seem to lack the selective properties inherent in end-organs subserving other modes of sensibility. Thus the notion has gained ground that in some mysterious way pain sensibility is a law unto itself and does not conform to the behaviour found to govern the operation of other sensory mechanisms.

Here again, we have to consider the purpose pain sensibility serves. If this be to signal the impending injury, the pain receptors must respond to whatever external agency threatens injury, whether this be mechanical, thermal or chemical. In other words, a pain receptor that did not respond to all forms of potentially harmful stimuli would be a receptor not adapted to its essential function, and is a structure we should not expect to find the organism endowed with. We are so accustomed to examine sensibility to pain with the point of a pin or of a needle that we have come to conclude that there is some essential biological relevance in cold steel, whereas in truth a steel point or an edge means neither more nor less to the organism than harmful degrees of heat and cold, or harmful degrees of mechanical stimulus. In short, a useful pain mechanism must respond equally to all potentially harmful stimuli from whatever kind of external agency. The one feature which does distinguish pain from other modes of sensibility

is the intensity of the responses and its dominating effect on consciousness, or rather on attention; but this also, surely, is a feature integral to a mode of sensibility possessing the purpose—if the word may be used—that all believe pain to subserve. There is nothing "primitive" about pain, as Head would have us believe, it is a highly sensitive and well-adapted form of sensibility.

In view of these considerations, the fundamental differences in the interpretation of the intensification during the stage of sensory restoration that we see in Head's and Trotter's papers gain importance. For Trotter, intensification is not a phenomenon comprehended within the Jacksonian doctrine of release of function, but an essentially pathological consequence of injury to the nerve. It attaches mainly to cold and to pain. Under normal conditions thermal stimuli at both extremes tend to elicit pain rather than purely thermal sensations. Both heat and cold become burning and with the appearance of this painful element the purely thermal component in the sensation wanes and disappears. Therefore, it may be argued, a sensation of "hot" is a compound of heat and pain, of extreme "cold" one of cold and pain. Therefore in a recovering area intensification is due to the association of cold and of intensified pain. Since the sensation of true heat returns relatively late and when pain intensification is waning, intensified heat is not prominent. According to this view intensification is essentially a phenomenon attaching to pain, whether this is elicited by stimulation of end-organs or of the regenerating nerve fibre itself. Trotter attributes it to nerve fibre stimulation, and postulates an increased sensibility of the regenerating nerve fibre. This increased sensibility is in turn ascribed to the imperfect insulation of the nerve fibre and to its constant irritation by the surrounding somatic tissues of non-neural character.

Trotter's views on the insulation of the nervous system have been fully developed in other papers (1926, 1928). It is the fact that not only is the central nervous tissue completely insulated from non-neural tissues by its meninges, but the peripheral nerve fibre is equally effectively insulated by its neurilemma sheath and nowhere makes contact with non-neural tissue except in the case of the naked nerve endings in the skin which constitute the receptor end-organs for cutaneous pain. When, as after amputation, this insulation is broken down we see the extravagant proliferation of axis cylinders and the brisk reaction of non-neural tissues by which these skeins of naked axis cylinders become surrounded in the formation of the familiar amputation neuroma. The painful phenomena

of the neuroma and of the phantom limb are other indications of this incompatibility between neural and non-neural tissues, and it is to this factor that Trotter looks to account for intensification of pain sensibility during the stage of nerve fibre regeneration. The new axis cylinder is thus regarded as subjected to constant subliminal stimuli and put in a state of increased excitability. Thus, in judging between the hypotheses of Head and Trotter, we find the former invoking a purely abstract conception that takes no account of the behaviour of living tissue, the latter invoking those facts of clinical and pathological observation that, even though they be not yet provedly applicable to the problem in hand, at least accord with what we know of the reactions of living tissue to injury.

IV.—Boring's Experiment in Nerve Division.

The discrepancies of observation and of theory apparent in the work we have considered led Boring to repeat upon himself the experiment in nerve division, choosing the anterior branch of the internal cutaneous nerve of the forearm ("Cutaneous Sensation after Nerve Division," *Q.J. Exper. Physiol.*, 1916, **10**, 1). Boring believed that he was better placed than his predecessors to assess alterations of cutaneous sensibility in virtue of the fact that he was a psychologist, a belief that he sets out at some length. It certainly led him to long introspective comments upon the different sensations he experienced in response to the stimuli employed; comments that sometimes leave the reader uncertain as to what precisely was experienced. Further, the branch of the nerve divided yielded a very small area of sensory change; one scarcely adequate to do justice to the psychological acumen lavished upon it. Nevertheless, Boring's observations are of interest in the light of those already discussed.

In general, he confirms Trotter's account of the sensory changes immediately produced by nerve section, and also of the successive sensory states revealed during the process of regeneration. He found a central region of cutaneous anæsthesia surrounded by a zone of progressively deepening hypoæsthesia to all forms of cutaneous sensibility. The outer margins of this were very ill-defined and irregular. Deep sensibility to pressure and to pain remained intact, so also did one-point localization and two-point discrimination: functions that Boring regards as wholly subserved by subcutaneous pressure endings. Recovery of sensibility was uniform in rate for all modes of sensibility affected, heat being somewhat delayed. Pain, cold and heat all showed intensification and peripheral reference. One point of importance, Boring's introspections do emphasize,

namely, the range of sensory qualities all commonly summed up under the term "touch." As Bazett remarks (1935), it is possible that in this regard we are letting words mislead us and that more than one sensory quality is in question here. The point is one that will be further referred to.

Boring gives reasoned arguments against the acceptance of Head's theory of a dual peripheral sensory mechanism. Some of these have already been dealt with, but there are others equally cogent that Boring brings forward. Like Trotter, he is unable to confirm Head's description of the sensory qualities of the intermediate zone, or the identity of these qualities with those displayed during the process of sensory restoration. In conclusion he assumes that a single sensory end-organ has a multiple innervation and that its stimulation leads to multiple impulses which reach the cerebral sensory mechanism there to undergo those processes of facilitation, summation and inhibition that we subsume under the term "integration." He appears to believe in the existence of inhibitory fibres, the division of which in a peripheral nerve may lead to hyperæsthesia or to abnormalities of localization.

More recently, Lanier (1935) has made some comparable experiments, using alcohol injection into cutaneous nerves as the method of physiological nerve section. Five areas of altered sensibility were produced in three subjects. He found that the area of altered sensibility to cold and warmth was more extensive than those to touch and pain, the two latter more or less approximating in extent. Signs of returning function first appeared at the end of the seventh week after nerve blocking. Thereafter pain, cold and touch sensibility returned at the same rate, warmth being greatly delayed. No evidence of any two-stage regeneration was observed. He attributes his finding of a greater extent of thermal loss to his more adequate technique. He found a central anæsthetic area surrounded by a zone of deepening hypoæsthesia to all forms of cutaneous sensibility, including touch. He confirmed Trotter's finding in respect of the intermittent occurrence of hyperalgesia in the hypoæsthetic zone prior to the appearance of regeneration phenomena. The intensification of the stage of regeneration he compares with the "injury" effect described by Adrian. The injured regenerating nerve is supposed to set up volleys of impulses of high frequency that lead—though how, we are not told—to thalamic "over-reaction." The chief interest of these observations is their general confirmation of the facts of observation recorded by Trotter and by Boring. In short, it may be said that no observer has been able to confirm the essential facts upon which Head's hypothesis rests.

It is clear that all this work has left unsolved, even in some cases unformulated, many of the problems of cutaneous sensibility. The range of sensations rightly to be spoken of as "light touch" has not been precisely defined, and the relations of this mode of sensibility to painless pressure still remains obscure. The basis of localization and of two-point discrimination, and the rival claims made for the cutaneous and the subcutaneous end-organs respectively in subserving these capacities still await final solution. Of the varying modes of sensibility so-called, it seems probable that some at least are not rightly so described but are concepts, or judgments based upon sensory material, e.g. two-point discrimination. It has even been suggested (Bazett, 1935) that pressure sense may be a concept, due to spatial summation of numerous subliminal tactile impulses. This brings us to the nature of the stimulus subserving what we call "light touch" or "contact sensibility" (Trotter). Blake Pritchard (1931) has criticized the notion of contact as a tactile stimulus, pointing out the mechanical deformation of the tactile end-organs—the essential element in adequate stimulation—involves more than simple contact. A degree of pressure on the skin adequate to lead to deformation of its surface is necessary to stimulate the tactile end-organ, and in this sense pressure leading to deformation is the adequate stimulus for the sensory qualities of touch and of pressure alike. The degree of pressure necessary to stimulate subcutaneous end-organs (subserving painless pressure) must, as von Frey and Strughold have pointed out (1927), involve a wider area of skin deformation than that which forms the threshold for light touch and must lead to the stimulation of cutaneous tactile end-organs over an appreciable area—possibly subliminal stimulation of many of them. Yet by the process of spatial summation a whole constellation of impulses may be set up in numerous fibres. Von Frey also records that anæsthetization of an area of skin markedly raises the threshold to deep pressure over the centre of this anæsthetic area. It seems possible, therefore, as Bazett has suggested, that the sensation we speak of as pressure derives from the activity of both cutaneous and deep sensory mechanisms, and is in the nature rather of a concept than of a primary sensation. Even light touch is not the simple matter our terminology assumes it to be. In fact, all the evidence points to the probability that we must have a physiologically sound notion of what constitutes the physiological *unit of sensory reception* before the outstanding problems of sensibility can be solved. Our pre-occupation in the past with the results of artificially stimulating single end-organs, and perhaps also our unfounded assumptions that single end-

organs only were being stimulated when in fact a pattern of end-organs of more than one order was being excited, have led to some confusion of thought and to an undue amount of speculation.

At the time the studies under consideration were made, relatively little was known of the fundamental neural processes involved, or—apart from the description of various forms of sensory end-organ in the skin and subcutaneous tissues—of the anatomical basis of skin sensibility. Head, Trotter and Boring were therefore compelled to attempt their generalizations while lacking much of the information on these points that we now possess. It is interesting to note what different lines of thought were pursued by them in this attempt. Head, strongly under the influence of Jackson's teachings, may be thought to have moulded his observations too ruthlessly within the framework of the abstract doctrine of release of function. Boring turned to Bernstein's speculations on central projection and diffusion to provide the integration of sensory impulses. Trotter approached the problem with a surgeon's familiarity in the handling of human tissues, and with an appreciation of the reactions which must ensue from the damage he was inflicting upon them when he divided nerves. Therefore he sought to account for some of the most striking phenomena resulting from nerve section in terms of the pathological reactions of injured tissue. This is seen in his account of the initial hyperalgesia and of the later intensification, where he expressed views that were later to be developed in his papers on the insulation of the nervous system (1924, 1926, 1928). These views have received scant attention or understanding from subsequent workers in this field, though numerous observations suggest that we may yet have to return to them. Thus, the differential behaviour of different categories of sensory nerve fibres under injuries of various kinds (pressure, nerve blocking by novocain), and the observations of Lewis on cutaneous hyperalgesia following skin injury, all indicate that disordered patterns of sensory innervation may be the product not solely of physiological or of anatomical factors but of pathological tissue reactions.

In another respect, Trotter's more realist attitude promises to find confirmation: namely, in his views on the nature of sensory hypoæsthesia. He expressed the view that any satisfactory theory of cutaneous sensibility must account for this phenomenon and once we abandon, as we must, Head's explanation of hypoæsthesia as the normal function of a special protopathic system of nerve fibres and end-organs, some other account of it must be provided. Trotter says: "it may be supposed that the sensi-

tiveness of the hair bulb is dependent upon the number of nerve fibrils going to it and possibly also on their reaching it from different directions, so that the maximal neural disturbance shall be produced by movement of the hair. Suppose now the numbers of fibrils conveying impulses away from a given hair situated in a region where the supply of two nerves overlaps, be considerably reduced by division of one of the nerve trunks, it is clear that the normal amount of neural disturbance can only be produced by a greater movement of the hair than is usually necessary; that is to say the hair bulb must be more firmly pressed on for a touch impulse to be originated, or in terms of sensibility the threshold of the touch spot is raised" (Trotter, 1909, p. 219). It is just such an arrangement that Weddell's recent observations have revealed, while in respect of pain Woollard has provided evidence that hypoalgesia is similarly caused. Clearly, such a generalization cannot explain the hypoæsthesia that may ensue upon lesions of the spinal cord and brain. This presents a separate problem. Yet another problem now exercising the minds of the investigators of the electrical activities of sensory nerve fibres finds its first formulation in Trotter's pages: namely, his finding of the increased excitability of the regenerating nerve fibre and of the possibility of eliciting from direct stimulation of the nerve trunk specific sensations of touch, pain and of cold and warmth when the appropriate stimuli were applied to the nerve trunk. This foreshadowed the specific activities of sensory nerve fibres subserving the different modes of sensibility that the observations of Gasser and Erlanger, and of Heinbecker, Bishop and O'Leary, to be later referred to, have revealed by other methods. In fact the confirmation of more than one of Trotter's inferences and findings has already begun.

In brief, in view of the richly suggestive character of Trotter's writings upon cutaneous sensibility it is striking how little influence they have exerted, and the cynic might submit that this is because he coined no new words to adorn his exposition. The sway exercised upon the imaginations of neurologists and physiologists by the words "epicritic" and "protopathic" may have had not a little to do with the continued currency of the hypothesis which was their setting.

Finally, of the many investigators of the sensory changes following cutaneous nerve division only one, Pollock (1919), has drawn attention to a phenomenon of sensibility in the area of returning nerve function that must have an important bearing upon the sensory qualities of the intermediate zone. Pollock, like Lanier, found that at the end of the seventh

week after nerve division the periphery of the area of altered sensibility began to shrink at its edges and to regain sensibility to pain. This appeared at a period before regeneration was possible, and must have been due to the invasion of the denervated area of skin by nerve fibres from adjacent areas of supply. Resection of the nerve originally divided did not abolish this newly appearing pain sensibility. Thus, the sensory qualities of the area of altered sensibility, during the stage of regeneration cannot be wholly attributed to the latter process. Recent experimental observations by Weddell, Guttmann and Guttmann (1941) confirm Pollock's surmise.

PART II.—PHYSIOLOGICAL AND ANATOMICAL OBSERVATIONS.

The problem unfolded by the clinical experimental studies we have been reviewing is manifestly a large one, but, as Sherrington has phrased it in another connection, "it has the interest that, large as it is, it yet—to speak *more Hibernico*—is larger still." So far, what we have been considering are gross phenomena capable of direct observation. Of the complex neural processes that underlie normal sensibility on the physiological levels they tell us very little, and while clinical studies may yet amplify and modify the facts of observation as recorded in the first part of this review, it seems unlikely that we can look to them to throw light upon the nature of much of the nervous activity involved. For this we must turn to the experimental physiologist with his command of instrumental methods of analysis and his greater choice and control of material.

The researches of Sherrington (1939) have served to define the motor unit of function, the motoneurone, and this appears to be "the motor nerve cell and the packet of muscle fibres, 150 or more, that it innervates. It is into these packets that the reflex is found to fractionate its muscles."

So far we have heard nothing of the sensory unit of function. The studies of Head, Trotter and Boring, and of those earlier workers who identified and examined the activity of cutaneous end-organs, appear to take for granted that the single cutaneous end-organ together with its conductor is the physiological unit of sensory function. Yet if we may draw any inferences from the nervous management of movement, and the nervous system does behave consistently throughout its range of activities, it appears possible, even probable, that the sensory unit consists of all the end-organs supplied by a single posterior root fibre. If this be so, the physiological unit would be a pattern of end-organs in at least two dimensions. Further, bearing in mind that our so-called tactile sensibility under normal conditions is probably a function of combined cutaneous

and deeper afferents (light touch and pressure endings), the receptor unit may be a three-dimensional apparatus of more than microscopic dimensions. It is interesting to speculate that in such an apparatus we may find the basis of local sign in sensation: a quality somewhat difficult to account for as long as we regard a single punctate sensory end-organ as the unit of function. Indeed, it would seem premature to speculate as to the basis of localization of cutaneous sensibility until we know in what the physiological unit of receptor function consists. Numerous other points equally demand elucidation: for example, whether the end-organ has a single or a multiple innervation, whether the sensory nerve fibre innervates more than one end-organ, the validity of Müller's law of specific nerve energy in the light of the most recent observations; the roles played in the various modes of sensation by end-organs, nerve fibre, central mechanisms, by the nerve impulse and by the central excitatory states respectively. These problems call for all the resources of minute anatomy and of modern physiological methods for the analysis of sensory processes. During the past few years a great body of information has been derived from these sources, and this has made it seem probable that the earlier studies of cutaneous sensibility discussed in the first part of this review were in some respects ill-placed to throw light upon the nature of normal sensory function, valuable as they have been in the formal description of the modes of sensory change following lesions of cutaneous nerves. They were based upon the punctate stimulation of single end-organs and upon the assumption, implicit if not explicit, that the single end-organ was the functional unit and the punctate stimulus a physiological one. By its artificial simplification, this method not only falls short of what is required, but may easily be misleading. Trotter clearly avowed his awareness of this danger.

In this field, also, we have to remember that to deduce from a study of the symptoms of lesions the normal functions of the structures injured is a complex and by no means direct problem.

V.—The Electrophysiological Study of Sensory Function.

The assessment of the results of modern electrophysiological methods is not easy for the clinical neurologist. This field of work is a highly specialized one which he will enter with diffidence and tread with circumspection, yet ready to view critically the large claims that are so apt to be made by enthusiastic exponents of new methods. Nevertheless, if it be true, as the French aphorism hopefully expresses it, that " ce qui se conçoit

bien, s'énonce clairement," he may hope to gain some light from the study of recorded observations, and he may even in virtue of his familiarity with other lines of attack upon the problems of sensory function, have a peculiar advantage in applying the fruits of special methods to their elucidation.

The foundation of this line of approach consists in the analysis of the nerve impulse: that is, its excitation by stimulation of receptor organs or of the nerve fibre itself: its potential value, its characteristic frequencies, and the modifications imposed upon it by the nerve channels in which it runs. This analysis has been made possible by instruments which not only register the potential change that constitutes the nerve impulse, but also amplify it sufficiently for its recording and measurement. The earlier workers (Keith Lucas, Adrian) employed the capillary electrometer. Later the moving iron oscillograph of Matthews and the inertia-free cathode ray oscillograph (Forbes, Gasser) were devised and, employed with vacuum tube amplifiers of increasing power, have revealed in end-organ and nerve fibre electrical phenomena not earlier discernible. In the monographs of Adrian (1928, 1935) and of Erlanger and Gasser (1937), the reader who is interested will find descriptions of these various forms of apparatus.

The original studies of the properties of end-organs and of nerve fibres were carried out by Adrian and his co-workers (Adrian and Bronk, Adrian, Cattell and Hoagland, Adrian and Zotterman). Later, Gasser and Erlanger and others took up the analysis of the compound potential changes in nerve trunks, determining the various fibre components involved and relating them to specific sensory activities.

Whether studied in an afferent or an efferent nerve, the individual nerve impulse is a remarkably constant and unvarying phenomenon. While impulses may vary in their potential value and their conduction rate, and in the sequences in which they occur, they display throughout the entire range of nerve fibre activities no qualitative differences, so that the notion of nerve impulses of specific character finds no support.

The conduction of the nerve impulse is the essential function of the nerve fibre. The impulse consists in a wave of electronegativity that passes along the fibre, leaving in its wake a transient phase of refractory state during which no further impulse can follow. Any prolonged activity of the nerve fibre is therefore necessarily rhythmic, the maximal frequency of nerve impulses being determined by the duration of the refractory state.

The stimulus, whether it arises in a sensory end-organ or from the

direct stimulation of the nerve fibre, acts by setting up in the fibre a local and non-propagated excitatory state. When this reaches a certain threshold value—peculiar to the fibre in question—an impulse is set up and is, for that fibre, of constant and unvarying value (potential). This is expressed in the statement that there is an "all-or-none" relation between the stimulus and the propagated activity it excites in the nerve.

Whatever we understand by Müller's law of specific nerve energy, it does not apply to the simple nerve impulse as such, for this is found to possess no specific qualities. Whether set up by end-organ or nerve fibre stimulation, and whether subserving motor or sensory function it does not vary in essentials. Therefore, when Head states, as we have seen, that "each impulse is stamped with the characteristics peculiar to the organ in which it has arisen," the notion—essential to his theory—is seen to be untenable.

Yet while the exciting stimulus cannot grade the intensity or influence the essential character of the impulse, it can determine the total activity of the nerve fibre by controlling the number and frequency of impulses set up, subject always to the limitations imposed upon the nerve fibre by its refractory state and by its rate of adaptation.

The essence of a stimulus adequate to set up nerve impulses is that it should produce a local change in the nerve of sufficient gradient, and a stimulus of progressively increasing strength is more potent than a constant stimulus. Thus direct stimulation of the nerve fibre by a stimulus of constant strength rarely sets up more than a single impulse, for the fibre rapidly becomes adapted, the stimulus falls below threshold value in consequence, so that by the time that the refractory phase following the initial impulse has passed off, it has become inadequate.

A somewhat different state of affairs is revealed by Adrian's studies (1928) of the sensory end-organs in skin, subcutaneous and muscular tissues. When the nerve fibre is stimulated physiologically through these normal channels a sequence or volley of impulses is commonly set up in the nerve fibre.

A considerable number of different types of sensory end-organ in skin and deeper somatic tissues has been described. Some of these have been identified as subserving specific sensory functions, but the precise sensory correlations of many of them remain undiscovered, or at most but the subject of surmise. At the present juncture all that we have to consider are the general qualities exhibited by sensory end-organs. In the matter of adequate stimulus we have a group (tactile, pressure and postural) for

which the stimulus is mechanical deformation, and this probably acts by stretching the terminal part of the sensory nerve fibre within the end-organ. Another group, heat and cold spots, respond to exchanges of heat at the body surface: the heat spots to additions, the cold spots to subtractions of heat, and not to temperature scale variations as such. A third group, of which the pain receptors are the striking example, ~~respond to example,~~ respond to mechanical, chemical and thermal stimuli. The purpose of this wide range of response on the part of the pain end-organs has already been discussed. Thus, four primary modes of cutaneous sensibility are generally believed to occur; touch, warmth and cold and pain. Closely associated with these are deep pressure and pressure pain; functions of subcutaneous end-organs.

Attaching to sensory end-organs of all forms are qualities which suggest that we may regard them as modified nerve fibres. They can be made to give frequencies of discharge up to the limiting capacity of the nerve fibre. Their rapidity of adaptation to stimulus varies from type to type, being rapid in tactile receptors, less so in the postural (muscle spindle) receptors. These qualities are so graded that the nerve fibre cannot be pushed beyond its capacity: that is, the fibre can carry impulses of a frequency as rapid as the end-organ can evoke in it. Similarly, the slower rate of adaptation of the end-organ allows it to set up sequences of impulses. The muscle spindle which is responsible to stretch of muscle is so slowly adapting that it sets up sequences of impulses of relatively long duration, while the rapidly adapting tactile end-organ may upon minimal stimulation adapt so rapidly that only a single impulse is set up. Adrian, Cattell and Hoagland (1931) made a skin-nerve preparation in the frog containing but a single sensory nerve fibre, supplying tactile end-organs to a relatively wide area of skin. They found these end-organs to be rapidly adapting, impulses being set up only during the actual movement of the skin. Repeated skin stimulation (by an intermittent air blast) set up impulses of high frequency and long duration, the frequency reaching a rate of 200 per second. The last-named mode of stimulation gave rise to none of the reactions commonly associated with pain, and it seems therefore that the end-organs excited by this mode of stimulation are specific for light touch and do not subserve pain. Another point of interest is that, as the sensory nerve fibre branches distally to supply several end-organs, so stimulation of a single receptor sets up impulses not only in its own conducting fibre, but also impulses of identical frequency and character that pass distally (antidromically) down the other branches of the parent

nerve fibre to influence the activity of end-organs not themselves subject to stimulation. The fibres concerned appear to belong to the β fibres in Gasser and Erlanger's "A" group of large myelinated fibres, to which reference will be made. In a subsequent investigation, Cattell and Hoagland (1931), on the same type of material, found the tactile end-organs rapidly adapting, and found the end-organs that are antidromically reached by impulses have their excitability reduced. This important finding suggests that the physiological unit of sensory function—or of sensory reception—comprises all the end-organs innervated by the branches of a single posterior root fibre: the stimulation of any one leading to the modification of the activities of every other. That is, the unit appears to be a skin area that—even in the frog—may cover 100 square millimetres.

The end-organs subserving pressure are less rapidly adapting than those subserving purely tactile sensibility, and with a steadily increasing pressure on the skin set up in the nerve fibre a sequence of impulses of waxing and waning frequency. The central responses to light touch and to pressure also differ, in that light touch remains a discontinuous, or intermittent, sensation however rapid the frequency of stimuli, while pressure is a continuous sensation.

The impulse response to stimulation of pain endings in the skin shows characteristic features. To a penetrating pin-prick, the initial sensation is one of painless touch and this is accompanied by a brief outburst of impulses. As penetration goes deeper, the impulses resume—or continue—at their original amplitude but with increased frequency, and a long after-discharge of impulses follows the cessation of stimulation.

The initial sensation of light touch that ensues upon minimal degrees of pin-prick has led to the suggestion that pain receptors serve both a tactile and pain function. The weight of evidence seems against such an assumption and in favour of the specificity of the pain end-organs, for in areas of skin containing nothing but pain fibres and their endings (Woollard, Weddell and Harpman, 1940), this initial sensation of touch is not felt. When present, therefore, it may be due to the concomitant stimulation of tactile endings. Further, the persisting quality of the pain of injury has led Adrian (1935) to suggest that the rapidly-adapting mechanism that subserves pricking pain cannot also subserve the persisting pain of injury. Further reference to this point may be deferred till we come to consider Woollard's work. In the meantime, we may emphasize again, as in the opening pages of this review, the fallacies latent in the tendency to postulate multiple peripheral mechanisms to account for obscure aspects of sensory function.

Other observations of Adrian suggest that the volley of impulses that traverse the length of a nerve fibre have imprinted upon them features dependent upon the anatomical characters of the fibre. For example, in many instances the impulses subserving pain are of small potential and slow rate of conduction, suggesting their carriage in small fibres. Ranson (1931, 1935) believes that the small unmyelinated fibres of the posterior root that enter Lissauer's tract in the cord subserve pain, and with Billingsley (1916) found that stimulation of these fibres in the experimental animal yielded reactions indicative of pain. Woollard's work also indicates that small unmyelinated fibres may play a part in pain conduction.

These observations lead us to ask whether variations in fibre size, in amplitude of potential and in rate of conduction have significance in the study of sensory function, and we are thus brought to the second phase in the electrical analysis of nervous sensory activity: that undertaken by Gasser and Erlanger (1937) and by Heinbecker, Bishop and O'Leary (1934, 1934,1935) who have investigated what is known as the compound action potential by means of the cathode ray oscillograph.

Gasser and Erlanger find that if the sciatic nerve of the bull frog be stimulated electrically at an increasing intensity all the component fibres of the nerve are finally thrown into activity. These fibres show different grades of excitability, differences in the amplitude of their potentials, and differences in their conduction rates; that is to say, as the stimulus gains in intensity, fibre after fibre fires off a sequence of impulses. This summed activity is reflected in the compound potential record. By the study of the record, it has proved possible to analyse the fibre composition of the nerve and to classify the fibres into types. Inferences have also been drawn as to the functional significance of the types thus differentiated. In comparable studies Heinbecker, Bishop and O'Leary have confirmed these observations on mammalian and human material, though they adopt a somewhat different nomenclature and basis of fibre classification.

To understand this work it is necessary to depict diagrammatically the compound potential and to name its component elements.

The compound potential shows three main waves, A, B, and C. The A wave is the largest and most rapid and has three components α, β, and γ. The B wave is smaller and of longer duration, and after an interval is seen a long drawn-out wave, C. Electrical analysis and histological control reveal that the fibres responsible for the A wave are the largest in diameter and the most rapidly conducting, and from the place they occupy in the record must have the lowest threshold of excitability. At the other

extreme are the small, least excitable and most slowly conducting fibres. The fibres producing the B wave are intermediate in these qualities. (Fig. 3.)

The functional correlations of these three main fibre groups have been determined by different methods: namely, (i) by the correlation of fibre size with the distribution of nerve endings in the relevant area of skin; (ii) by the comparative response to nerve blocking as judged by potentials and by sensory responses in the human subject; (iii) by the measurement of conduction rates of the impulses set up by stimuli exciting different modes of end-organ; and (iv) by the determination of the sensory qualities

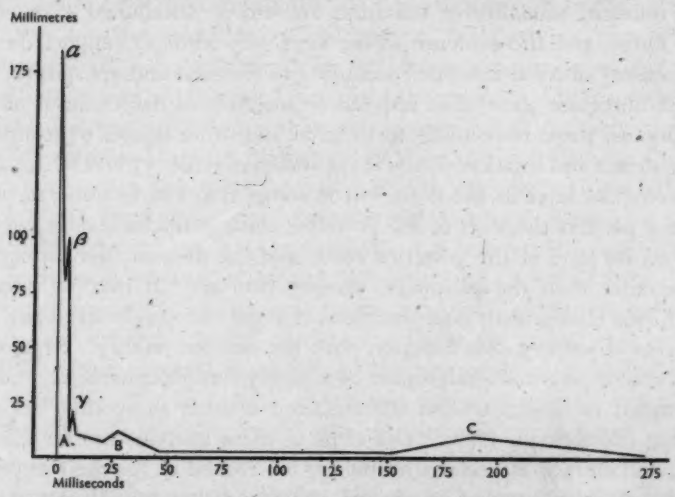

FIG. 3.—The action potential of the bullfrog's sciatic nerve transferred to linear coordinates. The starts, crests and notches of the A, B, and C elevations, in their correct temporal positions are joined by straight lines. Ordinates, amplitude in mm.; abscissæ, time in millisecs. (From "Electrical Signs of Nervous Activity," Erlanger and Gasser, 1937.)

of the responses to stimuli graded to excite different components of the nerve. From these various studies the present state of opinion appears to be as follows. To cocaine blocking of the nerve, the fibres go out of function progressively in the inverse order of size; C, B, and A. On the sensory side, the different modes go out in this sequence: cold, warmth, pain and pressure, or according to other observers: pain, cold, warmth and pressure. The fibres subserving pressure are the largest of the sensory components of the nerve, those subserving postural sensibility being of much the same order. It seems that afferent fibres stimulated by

mechanical deformation of their end-organs (touch, pressure and posture) are widely distributed through the A range. They are the last to be blocked by cocaine. Vibration sense goes before light touch, then pressure follows, and it seems likely that both the former are subserved by fibres of a larger average diameter than those subserving pressure. Warmth and pain are subserved by fibres slightly larger than those for cold, but also by the smallest C fibres. Pain is served by a wide range of fibre sizes, and some pain (delayed pain) is conducted by the C fibres, which remain active when all other fibres have been blocked. Cold is subserved by the narrowest range of fibre sizes. On the whole the fibres associated with each different modality of sensation are widely distributed through the fibre range, and the evidence so far as it goes tends to support the view that sensory fibres are grouped according to function and are specific. The fastest fibres are those that respond to mechanical deformation of their end-organs, those responding to thermal and other modes of stimulation being slower and smaller. Little is yet known of sensory fibres of the second physiological level in the cord, but it seems that conduction rate in the sensory path at the level of the posterior column nuclei is only one-third that at the level of the posterior roots, and the fibres at the former level are smaller than the peripheral sensory neurone. It may be added in conclusion that present interpretations of these various electrical and other analyses of sensory fibre function have not reached finality. Some of the most recent potential analyses are of a highly complex character, and have attempted to determine the afferent fibre systems subserving tickle and itching (Zotterman, 1939). The steps of these analyses are far too complex, and employ a special terminology too recondite, for their assessment by the clinician, and an impression is aroused that possibly too much is being asked of the method in elucidating physiological function, at its present stage of development. Yet with a method already so fruitful and so steadily advancing in delicacy it would be premature to say that it will not provide an even greater harvest before its resources are exhausted.

In short, all these investigations still support the old idea that there are four primary sensory modes, touch, pain, cold and warmth, and probably also subcutaneous pressure and pressure pain modes. They have shown conclusively that the individual nerve impulse is not of primary importance in the determination of the final sensory effect, but that the sensory pathway *as a whole* has components specific for each mode of sensibility. Each component in the pathway contributes an element to this specificity: the end-organ with its selective excitability and adapt-

ability (factors that vary with each sensory mode) determines the mode of activity of the conducting nerve fibre (the frequency and duration of the volleys of impulses); the fibre itself in virtue of its size (which conditions its excitability and conduction rate) also imprints specific effects upon the impulses that traverse it; while, finally, the central destination of each specific sensory group of fibres, and the variations in the central excitatory states, act as the final determinants of the sensory effects. There is, therefore, a mode of specific nerve energy, not resident in the single impulse, but a product of the combined activity and morphology of each component of the sensory path. In this way, the four primary modes of cutaneous sensibility, combined with the sensory impulses received from deep somatic structures, afford support for the view that all the complex sensations experienced can be adequately accounted for as a central integration or fusion of simpler primary ones. The number of variables that exist, physiological as well as anatomical, the permutations and combinations of impulse frequency, duration and intensity, the number of fibres in action and the interaction of cerebral mechanisms offer an adequate basis for a wide range of sensory experiences derived from a few specific components. As Jackson pointed out, a few muscles can be combined in different ways to perform an almost infinite variety of movements just as the few notes of the octave can be combined and changed to produce an infinite variety of tunes. Probably then, the central mechanisms that subserve sensation on the physiological level can serve with equal efficiency to provide the whole range of sensory experience from the material provided by the mechanisms we have reviewed.

One other point of interest in the experiments of Heinbecker, Bishop and O'Leary (1934) may be mentioned in connection with an observation of Trotter's already referred to. Trotter found that in response to tactile, painful and thermal modes of stimulus the regenerating cutaneous nerve trunk responded by yielding all the appropriate modes of sensation, thus revealing specific sensory qualities in nerve fibres when excited in the absence of their specific end-organs. This finding is in harmony with what electrical analysis has revealed of sensory nerve fibres, but, in addition, the observers named find that direct electrical stimulation of an exposed human cutaneous nerve yields sensations of touch and pain, thermal modes of sensation not being elicited by this form of stimulus.

Throughout the observations thus summarily considered, the notion is implicit that local sign is not so much a function of the individual end-organ, as of the interaction of impulses of varying frequency and

intensity derived from the simultaneous and successive activity of numerous end-organs, working perhaps in patterns. Indeed, it seems that the important lesson to be learned is that we must not think of the individual end-organ and its fibre as the physiological unit of sensation.

So far, no direct study of the identity of *the physiological unit of sensory function* has been discussed though, as we have seen, Cattell and Hoagland's observations throw light upon the matter. The problem has recently been attacked by an ingenious method by Sarah Tower (1940). She asks, "What is to be considered the unit nerve ending: all the terminal tissue of one nerve fibre or the separately encapsulated portions of terminal tissue?" In the case of the rich formation of unencapsulated nerve endings in the skin that subserve cutaneous pain, the product of free branching of sensory nerve fibres, the question seems still more to call for an answer. In the frog's skin Adrian, Cattell and Hoagland (1931) found that appreciable areas of skin were innervated by the branchings of a single neurone. Tower (1935) found that in the frog's viscera a single afferent fibre may innervate an area of from 2 to 3 sq. mm. Her present investigation takes the rabbit cornea for its sensory field. The terminal ramifications of a single afferent fibre comprise a unit area of from 50 to 200 sq. mm., the area having sharply defined limits. If we regard these branches and the fibre from which they arise as a physiological receptor unit we have something remarkably like the motor unit already referred to. Activity anywhere within this unit area is found to influence the whole, but not to influence adjacent sensory units in the cornea. Adaptation and fatigue phenomena were confined to the unit, and an impulse generated in one point of the unit area appeared to spread throughout the area to alter excitability at other regions within it. Tower therefore concludes that "the sensory receptor in the cornea emerges as all the terminal tissue of one nerve fibre. This is a unit, activity in any part of which affects the whole . . . the corneal sensory mechanism appears as an aggregate of units and not as a continuum.

While it is clear that much evidence remains to be gathered, it seems highly probable that this finding expresses a state of affairs that obtains throughout the sensory receptive mechanism. The anatomical studies of Woollard all point in this direction. Before closing this brief summary, mention should be made of another series of investigations which bear upon the central destination of the pathway for tactile sensibility. Marshall, Woolsey and Bard (1937) explored the monkey's cortex to see if tactile stimulation of the skin evoked in any part of it electrical changes

that might be considered to indicate the arrival of the relevant impulses, and to localize the situation of the sensory cortex. Bard (1938) has summarized their findings as follows: the application of discrete tactile stimuli to any cutaneous area evokes in a well-defined cortical area well-localized potentials, and reveals a detailed topographical representation of the body surface in Brodmann's areas 3, 1 and 2 that follows the same general plan as the similar cortical representation of movements in the precentral convolution. This sensory representation is strictly crossed. They consider it probable that the cortical area thus revealed is the projection area of the thalamocortical fibres subserving tactile sensibility, and the potentials may represent the summed action potentials of these fibres.

VI.—The Anatomy of Cutaneous Sensibility

The punctate nature of cutaneous sensory end-organs has long been established on a sound anatomical and physiological basis, but while the various types of these receptor organs have been minutely described by histologists, the mode and pattern of their innervation has remained largely unknown. Yet a full understanding of their contribution to sensory function requires that we shall know the nature of their nervous connections. Within the past few years by the adaptation of the method of staining nerve fibres *in vivo* by methylene blue, Woollard and his collaborators and successors in this work have added greatly to our knowledge of the nervous structures present in the skin, and have clarified much that was obscure. These most fruitful researches initiated by Woollard before his premature and regretted death have been pursued by Weddell and others, and promise to resolve many of the outstanding problems in the anatomy and physiology of cutaneous sensibility. In truth it is clear that the anatomist must have the last word in this long search to reveal the sensory functions of the body surface, for where there is no structure there can be no function. At least two of the hypotheses considered in this review must be regarded as wanting in validity because the postulated foundation of structure upon which they are built has been found, by these investigations, to have no existence.

By a series of comparative histological studies, using vital methylene blue staining, in the dog fish, rabbit, monkey and man, it has been found that there is a remarkably constant pattern of sensory innervation in the skin. This is most complex in the monkey and man in respect of the variety of end-organs present, but throughout the series the general architecture is strikingly alike.

Deep to the skin, sensory nerve bundles are found which branch freely, sending ramifications in all directions to enter the skin. Therein they form two main nerve plexuses, deep and superficial. Thick and thin nerve fibres, both medullated and non-medullated, compose these plexuses, the deeper being on the whole composed of fibres of greater diameter. Within both plexuses fibres of varying calibre may be seen to run inside a single neurilemma sheath. In the skin of the rabbit's ear, thick fibres are seen to innervate hair follicles. Each follicle may contain as many as ten hairs, and as many as seven terminal fibres may innervate a single follicle. The ramifications of a single fibre may innervate as many as 300 follicles (Weddell, 1941*c*). Further, each follicle receives a dual principal innervation, receiving a main fibre from at least two parent stems. In addition to this hair follicle innervation, finer fibres from the superficial plexus are seen to shed their medullary sheaths, to become varicose and to branch repeatedly to form rich arborizations of naked and beaded terminals which lie below and between the epidermal cells.

In human skin the same deep and superficial plexuses are to be seen. The finer branches enter the stratum mucosum and stratum granulosum and, branching freely, provide the rich network of beaded terminals already described. Further, fine non-medullated fibres are seen to provide an "accessory" innervation to complex end-organs of various types in the skin, e.g. to Meissner's corpuscles and to Krause end-bulbs. These accessory fibres expand and form a skein in the end-organ. Thus each group of these end-organs receives a dual principal innervation and an accessory innervation (Weddell, 1941*b*).

The fine branchings which arise from the superficial plexus form a prominent feature in the skin. The branches from each parent fibre interlock with those from other fibres, but there is no continuity between overlapping arborizations. These fibres and those providing the accessory innervations are of the same morphological type, and for reasons to be considered, it is concluded that they constitute the anatomical mechanism of cutaneous pain sensibility. The arborizations arising from different parent fibres each innervate a roughly circular area of skin, of dimensions that vary from one body region to another. Thus, on the dorsum of the hand such a single area may have a diameter of no less than 0·75 cm.

The Meissner's corpuscles, which are thought to subserve tactile sensibility, are most thickly sown in the papillæ of the skin of the finger tips, one square millimetre containing as many as ten groups of two to three corpuscles. These organs are commonly thus grouped and are rarely

solitary. A "touch spot" as known to the physiologist consists of one or more groups of the corpuscles, and it is found that at least two main fibres, relatively thick and medullated, innervate each "spot." In addition each corpuscle has its fine "accessory" fibre. Krause end-bulbs, believed to subserve the sensation of cold, are similarly grouped and innervated, and it seems probable that a "cold spot" comprises one or more small groups of these endings, with a dual principal innervation and an accessory fibre to each end-bulb. Another form of end-organ, Merkel's disc, has been observed in the skin of the monkey's thumb.

It will be appreciated that this arrangement of end-organs in groups and in particular the groupings of naked nerve-endings in area and in depth, is that outlined by Trotter as governing the innervation of the skin. It provides an explanation of sensory hypoæsthesia, since immediately after section of a cutaneous nerve a given group of end-organs has less than its full innervation. During regeneration the full multiple innervation is only gradually restored. Thus stimulation of a given "spot" tends to set up less than the normal amount of neural disturbance. In respect of the free endings, the diminished number of endings and the absence of overlap has a comparable result in respect of painful sensibility. By novocain blocking, in succession, of two cutaneous nerves innervating adjacent areas of skin. Woollard, Weddell and Harpman (1940) found that the contiguous margins of tactile insensibility coincide, but that there is a gap of about 1·0 cm. in width between the adjacent margins of analgesia to pin-prick. In other words, as Head had found, the distribution of the pain fibres in a given nerve is more extensive than that of fibres subserving tactile sensibility. In this gap of 1·0 cm. width fibres and endings subserving pain overlap, and this narrow zone receives its pain fibres from two adjacent nerves. When, in this zone of overlap, one nerve is divided, the number of pain spots is found to be reduced and the threshold of pain sensibility raised. Weddell, Guttmann and Guttmann (1941) find evidence of similar overlap in the rabbit. For a given cutaneous nerve they find a central "autonomous" area supplied by the divided nerve alone, an intermediate" zone of overlap, and a maximal zone—comprising both the preceding—that constitutes the entire area of distribution of the nerve.

They also find that, shortly after nerve division, the intermediate zone begins to shrink peripherally, and find histologically that the reason for this shrinkage is the invasion of the partially denervated skin by advancing pain fibres from adjacent intact nerves. In other words, the early stages of apparent restoration of pain sensibility are due, not to regeneration of

divided fibres, but to growth of nerve fibres subserving pain in adjacent areas. As already mentioned, Pollock found a similar state of affairs in the human subject.

Another feature of cutaneous innervation revealed by all these observations is the dispersal in all directions of the nerve fibres that enter the skin. In this way they approach the region they are to innervate from widely different directions. Thus the fibre that finally reaches the centre of a given area may have further to travel than one that innervates its periphery. Hence, during the process of regeneration, the growing fibres have different distances to travel and cannot simultaneously re-form their former connections with their appropriate end-organs.

In addition to these histological investigations, Woollard and his co-workers (Woollard, Weddell and Harpman, 1940; Weddell, 1941*a*, 1941*b*, 1941*c*; Weddell and Glees, 1941; and Weddell, Guttmann and Guttmann, 1941) have carried out a number of physiological observations directed to the study of cutaneous pain sensibility.

It is found that the penetration of the skin by sharp needles may yield sensations of touch, pressure, cold, warmth, and pain, or—upon occasion—no sensation. Penetration of the skin is essential to the production of pain, and like many earlier observers, they find the pain to be of two qualities.

Thus, there is (i) an abrupt, brief, painful sensation that hurts relatively little, followed as penetration proceeds by (ii) a delayed pain of increasing intensity, like a small stinging area, and of slow waning. It may not reach its maximum for two seconds. The two pains may follow without an interval (phasic pain sensation) or an interval may separate them, this feature varying according to the body region stimulated. In respect of the different modes of sensation yielded by a prick, they note that the "first" pain is elicited on a penetration of 0·25 mm., "second" pain at 1·0 mm., cold at 1 to 1·5 mm., warmth at 1·75 to 2·5 mm., pressure at 2·0 to 2·5 mm., and—paradoxically—touch at 2·0 mm. penetration. This last result is not so odd as might at first sight appear, for an extremely sharp-pointed needle may well penetrate relatively deeply before causing that deformation of the surface of the skin that is the essential condition of the stimulation of a touch corpuscle: a consideration that deprives the argument that pain receptors may also subserve tactile sensibility of its force.

Further investigations showed that in areas of skin which subsequent examination revealed as containing only the free nerve endings already described, the only sensation yielded was pain. Both "first" and

"second" pain were localized with equal accuracy, and the discrimination of two successive pricks was achieved with accuracy when sufficiently far apart (1·0 cm.) to include the areas innervated by the branchings of two adjacent parent fibres: that is to say, when they were so placed as to set up separate impulses in two afferent fibres. Since, as we have seen, the pain mechanism is disposed in depth as well as in area with pain fibres lying in both deep and superficial plexuses (the final branchings arising from the latter), Woollard believes that both superficial and deep pain are subserved by a single neural mechanism. Deep pricks pass through the disposition of the mechanism in depth and stimulate not only superficial arborizations but also deep nerve fibre handles. He thus accounts for the greater intensity and diffuse character of deep pain on the basis of spatial summation.

Finally, pain appears to be subserved wholly and exclusively by terminal nerve twigs with free nerve endings, and he finds no trace of any other such arrangement of fibres in the skin, thus invalidating the hypothesis, to be later discussed, that there is a separate "nocifensor" system of cutaneous nerves of this morphological type.

We see, therefore, that the unit of pain reception appears to be, not a single pain spot, but all the branchings and free endings of a single parent fibre, disposed in area and in depth, and of a total volume of macroscopic dimensions. From what Tower has shown of the widespread activity within such a unit when one point of it is stimulated, we may probably find in this arrangement the basis of local sign in painful sensation. The more highly organized end-organs subserving other modes of sensibility: tactile (Meissner's corpuscles, Merkel's discs), cold (Krause's end-bulbs), warmth (Ruffini's endings), pressure (Golgi-Mazzoni and Ruffini endings) appear, as far as can be ascertained, to be arranged on a similar plan, and thus it seems probable that localization is achieved in respect of each modality in virtue of the massed arrangement of the individual end-organs and of the multiple innervation of each group of these organs.

A further word remains to be said of the "accessory" fibres seen in different types of cutaneous end-organ. Morphologically these resemble the fibres subserving pain, and Woollard suggests that they may by their presence there signal the advent of supramaximal and potentially harmful stimuli; that is, they may act as a form of "burglar alarm" in the ending. Their presence might also account for the wide range of stimuli that is capable of yielding a sensation of pain: a notion compatible with the specific activity of each type of end-organ.

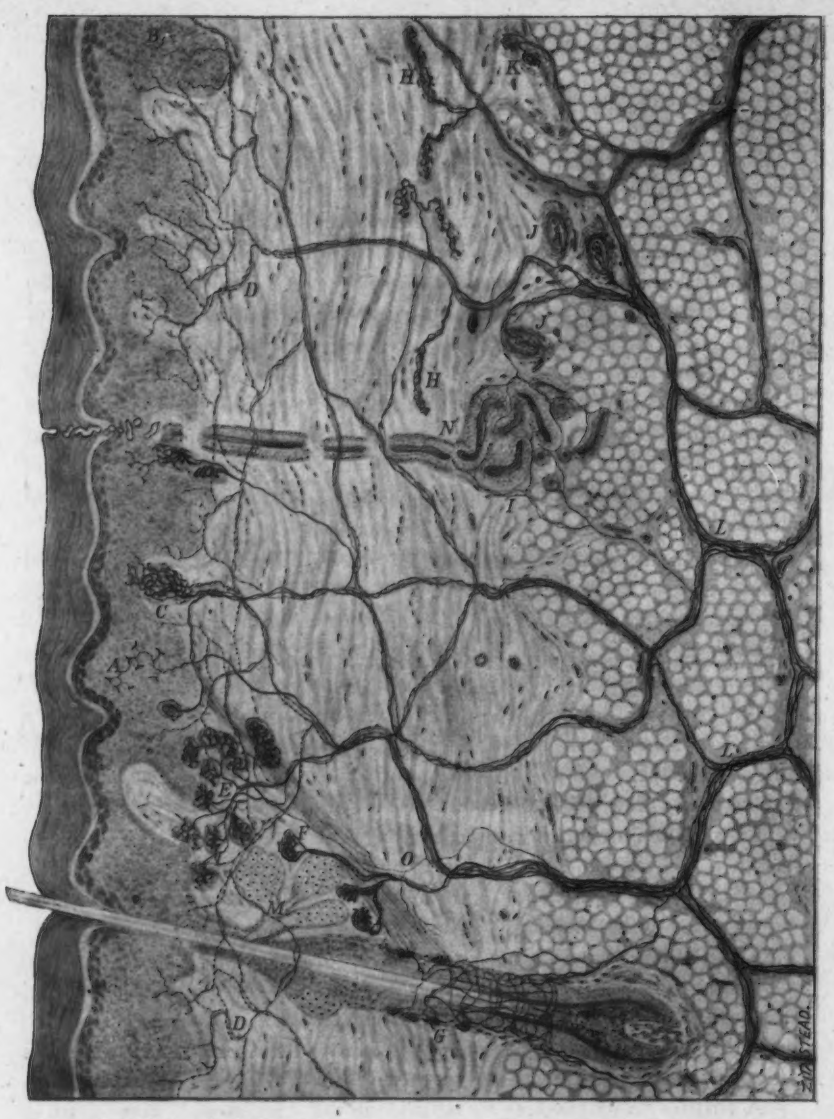

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FIG. 4.—Composite diagram showing the innervation of the human skin. A, Merkel's discs, subserving touch. B, Free endings, subserving pain. C, Meissner's corpuscles, subserving touch. D, Nerve fibres, subserving pain. E, Krause's end bulbs, subserving cold. F, Nerve-endings, subserving warmth (sometimes called Ruffini's endings). G, Nerve fibres and endings on hair follicle, subserving touch. H, Ruffini's endings, subserving pressure. I, Sympathetic nerve fibres innervating sweat glands. J, Pacinian corpuscles, subserving pressure. K, Golgi-Mazzoni endings, subserving pressure. L, Nerve trunks containing thick and thin fibres. M, Sebaceous gland. N, Sweat gland. O, Sympathetic fibres supplying arrector pili muscle. Drawing composed from methylene-blue and reduced silver preparations. The functional interpretations above are based upon observations by the writers. (From Woollard, Weddell and Harpman, *J. Anat.*, 1940, **74**, 427.)

Fig. 4 taken from the paper by Woollard, Weddell and Harpman (1940) represents the authors' conception of the innervation of the skin as seen in section.

Weddell and Harpman (1940) have also studied the sensory end-organs in deep fascia, periosteum and tendons, and their findings have some relevance to the problem of pain sensibility. They find three types of nerve ending in these structures: a freely branching system of fine fibres terminating in free endings, Vater-Pacini and Golgi-Mazzoni endings. Each of the two last receives the same fine "accessory" fibre that has been described in Meissner's and Krause's end-organs.

PART III.

Some Conclusions.

In a passage cited earlier, Head remarks that "between the impact of a physical stimulus on the peripheral end-organs of the nervous system, and the simplest changes it evokes in consciousness, lies the various levels of physiological activity . . . by the time afferent impulses reach one of those centres where they can form the underlying basis of sensation ~~they~~ they have been profoundly modified." Yet from what has been said, it seems clear that the physiological processes concerned are not what Head envisaged. Until the highest centres of sensory function are reached, the impulses subserving the four primary modes of cutaneous sensibility appear to travel virtually unchanged, and do not undergo the remarkable modifications in spinal cord or brain-stem outlined by Head. It appears likely from what we have recently learned of the innervation and grouping of sensory end-organs that the impulses in virtue of their multiple source in doubly innervated end-organs, and of their different frequencies and sequences, provide much more complex sensory material for integration than Head supposed, or could have known. It seems likely, for example, that local sign in sensation is subserved by the spatially and temporally dispersed origin of impulse volleys.

Of the further central modifications that sensory impulses undergo very little is known, though something can be surmised if we turn to the great deal that is known of the central nervous management of movement. The student of sensory functions most deeply versed in the work of Sherrington and his school is probably he who will see furthest into the physiological problems of sensation. In this connection, it may be suggested that no student of these problems can afford to neglect the article

on cutaneous sensation written in 1900 by Sherrington in Schafer's two volume textbook of physiology. The workers on cutaneous sensibility of the closing years of the last century saw deeply into the problems involved in tactile localization and discrimination, and their observations are only to be found assembled and critically examined in Sherrington's article. We may yet have to go back in thought to this relatively remote period in physiological history, and consider sensory functions in the light of what was then thought, and what is now known, before success rewards our efforts in this most complex of problems.

VII.—Problems of Cutaneous Pain Sensibility: The Nocifensor System.

No mode of cutaneous sensibility has been the subject of so much speculation and of such conflict of opinion as cutaneous pain. It has been spoken of as being of high threshold, as possessing receptors responsive to a wide range of stimuli, mechanical, thermal and chemical; as being subserved by two separate peripheral mechanisms—the one responsible for the brief rapidly developing pain of a prick, the other for the more slowly developing and longer lasting pain of injury; slow and fast pain fibres have been postulated each subserving different modalities of pain; according to Head the peripheral mechanism concerned is of "crude" function and "primitive" phylogenetic history, capable of eliciting maximal and ungraded sensations and endowed with no precise local sign; Trotter has emphasized the disproportion between stimulus and the overwhelming nature of the sensation resulting in consciousness; while the function of pain as protective, or as signalling impending injury to the tissues, has been widely accepted. In the field of electrophysiology comparable variations in view have been expressed.

There are, as Trotter has pointed out, limitations to the notion that pain serves a primarily nociceptive or protective function. Thus, to the lethal X-ray it yields no response, while some internal maladies of fatal issue are advanced beyond hope of treatment before they elicit any activity in the mechanism subserving pain. Yet in respect of trauma—and we are now considering *cutaneous* pain sensibility—it seems reasonable to agree that pain does signal impending external injury and thus serve a protective function. Again, as Trotter has emphasized, the stimuli adequate to elicit pain are of a quality less than necessary to injure the tissues, and so, if we accept the protective function of pain, we cannot reasonably speak of it as a high threshold mode of sensibility. The mathe-

matical and mechanical standards by which in the past we have tried to calibrate the threshold value of the pain receptors are, as has been suggested, wholly irrelevant to the organism. Further, the sensitivity of the cutaneous pain receptors to a wide range of stimuli is not a quality that, biologically considered, differentiates them from those subserving other modes of sensibility. This mechanism responds to potential noxa. We have agreed that it is its function to do so, and in this sense the response is not less specific than those of others receptors. Here again, we have to consider the biological relevance of different forms of adequate stimulus.

That these receptors also subserve tactile sensibility is a notion that we have seen to contain a fallacy, since in areas of skin deprived of tactile sensibility and containing only the specific endings for pain, no touch is felt. The penetration of the normal skin by a pin when it is progressive must sooner or later—and this according to the fineness or otherwise of the extremity of the pin or needle—deform the skin and thus stimulate both tactile and pressure nerve-endings.

Woollard's observations lend no support to the view that there are two peripheral mechanisms for pain. The wide area and appreciable depth of skin supplied by the arborizations of a single sensory parent fibre make it clear that a penetration of any depth by a sharp needle must " touch off " a number of pain nerve-endings and nerve fibre bundles. In the case of any given single stimulus of this order, no one can ever say within wide limits what amount of neural disturbance has been set up, that is, how many volleys of impulses in how many fibres have been excited. This point of view receives some confirmation when we consider what happens in an area deprived of overlap by the section of one of the two main nerves supplying an area of skin. The pain endings and fibres are found to be less numerous and the threshold raised. The hypoæsthesia is a natural result of the stimulation of fewer receptors.

A somewhat different problem—at least on a superficial view—is provided by the persistent hyperalgesia that follows minor damage to the skin. There are several indications as to how this may arise, but the most elaborate hypothesis is that advanced by Lewis (1936) who has postulated the existence of a special system of nerves which, acting in association with the pain nerve-endings, specifically subserves this sensory reaction. This he names the " nocifensor system."

Like Head's hypothesis, this one seeks to generalize clinical observations by supposing the existence of an anatomical mechanism of which no direct evidence is provided. In the course of observations carried out with

Hess (1933), Lewis noted the development of cutaneous hyperalgesia following local injuries to the skin. This hyperalgesia tended to spread over a relatively wide area surrounding the lesion and to endure for a matter of one or more hours. In normal circumstances, damage to the skin is the natural stimulus to the development of hyperalgesia, but under experimental conditions Lewis (1936) found that (i) crushing, freezing or faradizing tiny areas of skin; (ii) faradizing cutaneous nerve trunks—either through the skin or directly through subcutaneous electrodes, were equally effective.

The resulting hyperalgesia is a smarting soreness of the skin, spontaneous and on friction, and lends a peculiarly diffuse and longlasting pain on pin-prick, and when a needle is mounted on a flexible hair pin-pricks are felt "more often" over a hyperalgesic than over a normal area. The topography of the hyperalgesic area has certain characteristics. To a tiny skin crush there ensues an oval area of hyperalgesia, to faradization of a nerve the hyperalgesia may fill the entire cutaneous distribution of the nerve. Hyperalgesia develops progressively after a delay of seconds or minutes, according to the intensity of the stimulus, and waxes and then wanes over a period ranging from one to several hours before it finally disappears. Not all subjects appear to yield the reaction, at least upon the occasions on which they were tested to this end—though Lewis does not make this important qualification.

In a series of further observations, Lewis found that if an area of skin is anæsthetized before crushing, hyperalgesia does not develop until the anæsthesia passes off, when it appears in the usual way. Once it has ensued upon a skin crush, anæsthetizing the lesion does not abolish it. When the stimulus is faradization of a nerve trunk, blocking the nerve prior to, and proximal to the point of, stimulation delays the appearance of hyperalgesia until the block has passed off, when hyperalgesia develops as usual. But if before we stimulate the nerve we block it distally no hyperalgesia appears when the block passes off.

From the skin crushing experiments, Lewis concludes that the production of hyperalgesia must be due to the activity of cutaneous nerve fibres within the skin, the intensity, spread and rapidity of its development being incompatible with the simple notion of release and spread throughout the skin of a "pain-producing" (P-P.) substance. Further, the delay in appearance of the reaction until the previously imposed anæsthesia of the damaged piece of skin has passed off, also indicates a nervous mechanism; while, finally, the fact that, once established, hyperalgesia is

not abolished by anæsthetizing the lesion, indicates that a maintained flow of nerve impulses from the immediate region is not essential. From the faradization experiments he deduces that an ascent of impulses from the stimulated nerve to the central nervous system cannot be in question, since when the nerve is blocked above the stimulated spot—and no impulses can travel centripetally—impulses can still travel antidromically to the nerve-endings in the skin where they suffice, as soon as the block passes off, to elicit hyperalgesia. The prior blocking of the nerve below the spot faradized does not prevent the central passage of impulses, but does prevent their passage distally to the nerve-endings, and in these circumstances no reaction ensues. Therefore, hyperalgesia must be due to the setting up of an altered state in the skin co-extensive with the cutaneous territory of the nerve stimulated.

The train of processes he supposes to be set up by damage to the skin is as follows:

Damage to skin, local liberation of P-P substance.

↓

Stimulation of nerve endings in skin by this substance at the site of the lesion.

↓

Spread of nervous impulses throughout all or part of a cutaneous nerve distribution.

↓

Local liberation of more P-P substance at all endings of these skin nerves within this distribution.

↓

Lowering of threshold of all pain receptors in this area of skin.

↓

Passage of impulses centripetally along pain fibres to central nervous system.

↓

Hyperalgesia in affected area of skin.

It is the sole and essential function of the special system of cutaneous nerves concerned to cause the liberation in the skin of pain-producing substance, and the presence of this in the skin accounts for the persistence of the hyperalgesia, even when the damaged spot is anæsthetized and no nerve impulses are proceeding from it.

Lewis believes that the nerves in question cannot be the fibres and endings subserving pain because stimulation of a pain receptor yields a brief and accurately localized sensation of pain; a response he regards as impossible in the case of such a cutaneous nerve plexus as he envisages. The wide spread of the hyperalgesia he attributes to the richness of the arborization of the parent nocifensor fibres when they enter the skin.

He also speaks of the parent fibre as ultimately joining the posterior root fibres and entering the spinal cord.

Woollard's histological observations provide no evidence of the presence in the skin of any other system of branching nerve fibres with free endings than those demonstrably subserving pain, yet it is just such a system that Lewis postulates as present in addition to the pain-subserving fibres and endings, and just such a system that is found in fact capable of yielding a minutely and accurately localized sensation of pain. We see, therefore, that a nerve plexus can yield localized sensations, and that the only plexus of the kind known to exist subserves pain. There is no other. Another difficulty—if this were not conclusive enough—presents itself in the acceptance of Lewis's hypothesis. Let us try to construct a diagram of the nocifensor system, for if this has an anatomical existence it should be possible to represent it diagrammatically. At its distal extremity, the nocifensor fibre ramifies to form an arborization of free nerve-endings in the skin, while proximally it runs up in the sensory nerve trunk to reach the posterior root and spinal cord. Its further fate and function therein, we are not told, but all that the hypothesis requires is a cutaneous nerve plexus co-terminous with that of the cutaneous nerve within the territory of which it is found. No discoverable function can be conceived for a central prolongation of the nocifensor system into the central nervous system, for of itself the system subserves no sensory function, and its activities are locally engendered and locally executed in the skin. The endings of the nocifensor plexus appear to be both receptor and effector, for when damaged an ending sets up impulses which travel throughout the plexus to all other endings, which then act upon skin cells; undamaged, the endings become effector themselves. In short, there are insuperable objections to Lewis's interpretation of his observations.

Nevertheless, some generalization of the facts of cutaneous hyperalgesia is called for, and, it is submitted, this may be found within the scope of what we already know about the structure and functions of the sensory nervous system. In respect of crushes of the skin, two results may follow: the stimulation of nerve-endings and fibres subserving pain, and the liberation from the damaged cells of the skin of "pain-producing" substance. Taking the first, and most certain, of these factors, the evidence points to the following conclusions. The unit of sensory reception for pain (as for other modes of sensibility) appears to comprise all the endings arising from a single parent fibre (presumably a posterior root fibre). This unit may be of relatively considerable dimensions on the surface and is

also disposed in depth in the skin. Damage to any part of this unit affects the activities of the entire unit and may reasonably be assumed to set up a neural disturbance which arises from all parts of it. Further, as Adrian (1935) has shown, injury, particularly in sensory nerve fibres, sets up a rhythmic discharge in the nerve fibres. The discharge consists of a sequence of impulses of high frequency, sometimes of a recurrent discharge of from 2 to 20 impulses. How widely within the receptor unit this discharge may spread we do not know, but we may not assume that it occurs only within the limits of the actual crush.

That preliminary anæsthetization of the skin to be crushed delays the onset of hyperalgesia is inevitable; since inactivated fibres cannot be excited or impulses generated in them, and that subsequent anæsthetization of the crush does not abolish an already established hyperalgesia could be explained on the grounds given in the immediately preceding paragraph. The additional part played by released "pain-producing" substance in reinforcing the "injury discharge" may be mentioned but cannot be assessed, but if it is operative and involves a larger territory than that anæsthetized, it would tend to add its influences to those of direct nerve injury. In this connection, we may recall Trotter's emphasis upon the "naked" and non-insulated character of the nerve-endings subserving pain sensibility, which would render them peculiarly responsive to chemical stimulants within the skin.

In the case of the hyperalgesia ensuing upon nerve trunk faradization, the factors operative are somewhat different. Here there is no local damage to cutaneous nerve-endings, but these endings receive a succession of impulses from above that may conceivably lead to the liberation at their endings of "pain-producing" substance. Whether this substance excites the endings without injuring them, or whether it constitutes a trauma, we do not know, but it is an agent of a kind that we should expect to set up prolonged activity in pain nerve fibres.

That blocking of the stimulated trunk above the spot stimulated should delay the onset of hyperalgesia is inevitable, since hyperalgesia requires for its appreciation an open pathway from skin to cerebral sensory centres. On the other hand, blocking of the nerve trunk below the spot faradized prevents the downward passage of nerve impulses to the skin endings and the resulting liberation of "pain-producing" substance.

In short, there appears to be nothing in these observations that requires us to postulate the existence of a special set of cutaneous nerves. Woollard's observations provide convincing evidence that the system of nerve fibres in question is that subserving cutaneous pain.

Other sensory modalities also arise for consideration in connection with pain: namely, tickling and itching. As Blake Pritchard (1932) has pointed out, the word "tickle" embraces two sensations differing in quality and in mode of elicitation. There is the superficial tickle that ensues when a hair or cotton fibre rubs along the thin skin of the lip or entry of the nostrils, and the deep tickle that follows firm pressure with the fingers down the sides of the chest or in the axillæ. Superficial tickle requires a rapid sequence of discrete stimuli to tactile receptors, and in many regions of the body a wisp of cotton-wool drawn very lightly over the skin will elicit it. Pritchard has found that this sensation is abolished in cases of spinal cord lesion, e.g. syringomelia, where cutaneous pain is abolished and light touch intact. On the other hand, when there is an intensification of cutaneous pain, e.g. over the distal parts of the limbs in some cases of polyneuritis, he found superficial tickle intensified.

This suggests that tickle is a compound of touch and pain, or, as Pritchard believes, a minimal expression of pure pain, produced by the summation of a series of subliminal stimuli. The presence of an accessory fibre in each hair follicle, where it probably subserves pain, may have significance in this connection. Itching is probably also a variant of pain sensibility.

There are other problems of persisting pain following lesions of peripheral nerves that as yet have not found elucidation. Perhaps the phenomena of causalgia is the most striking of these. They may find their solution in the light of what we know of injury discharges in sensory nerves, and of the differential response to injury of the fibres subserving the various modes of sensibility.

In the category of spinal reflex reactions, Sherrington has spoken of what he calls "prepotent" reflexes: reactions that obtain control of the reflex paths and effector organs when these are played upon by multiple peripheral stimuli of different orders. Such a reaction is the nociceptive flexion reflex. In pain we may have on the sensory side a "prepotent" mode of sensibility, one that from its biological function has come to assume the dominating influence it has upon the sensorium. Just as its threshold is that appropriate to its function, so the sensory quality of pain is also appropriate to its end. Thus, we do not need to think of pain—as we experience it—as characterized by being a response disproportionate to the stimulus that excites it. Both threshold and response are in fact adapted to the role pain plays in the life of the organism. In short, pain is not the striking exception we often regard it as being to the rules that characterize other modes of sensory function.

VIII.—Some Problems of Tactile Sensibility.

In Head's hypothesis the localization of all modes of cutaneous stimuli is especially associated with tactile sensibility. As a component of his epicritic system it was a function of touch to correct the erroneous localization of painful and protopathic thermal sensations and to impart correct localization to them. How this was achieved was not described, but even for those who no longer subscribe to Head's hypothesis, the notion of touch as a peculiarly localizing mode of sensibility has lingered.

Thus, Blake Pritchard (1931) regards light touch (or light pressure, as he calls it) as being primarily and essentially a localizing function, which together with proprioceptive postural sensibility mediates spatial perception and discrimination. He bases this conclusion both on theoretical considerations and upon an experiment in which he used radiant heat as a stimulus. He did this to avoid that deformation of the skin which under normal conditions necessarily evokes tactile sensations. He used a heated platinum loop and believed that he was stimulating "heat spots" only, and whereas, using von Frey's hairs as a tactile stimulus he obtained an average error of 0·5 cm., with the heated loop there was an average error of over 1 cm. Lewis repeated this experiment, using a beam of light focussed upon the skin so as to cover an area of 4 to 5 mm. in diameter and there developing a temperature of 38° or 39° C. Pritchard made no skin temperature estimations, so that whether he was stimulating heat spots alone or also pain spots cannot be stated. Lewis obtained an average error of 1 cm. or less. Using a needle prick, Lewis found an error of less than 1 cm. Woollard's observations with needle prick are comparable with Lewis's. He found that two successive stimuli can be recognized as having been applied at different sites at a distance of 1 cm. on the forearm, 0·5 cm. on the palm and 1 mm. on the finger tips. It is true that in the last-mentioned experiments, tactile sensibility was present, but they appear to indicate that its presence had no influence in increasing the accuracy of localization of painful stimuli.

Tactile sensibility is essentially a form of pressure sense, since deformation of the skin is the adequate stimulus to its receptors. Even the bending of a hair when the skin itself is not touched, involves deformation of the tissue immediately surrounding the hair bulb. Yet it has sensory qualities that distinguish it from deep pressure. Trotter has described the "pat" that constitutes a sensation of touch, and has said that introspectively it can always be differentiated from the sensation aroused by continued pressure. Electrical analysis confirms this distinction, as Adrian and his

co-workers have shown, and it may be concluded that the two sensory modes possess end-organs and conducting fibres of specific function in each case. Stimulation of tactile receptors even when repeated at high frequency always yield discontinuous sensations, while increasing pressure yields a continuous sensation.

Yet the stimulation of a touch spot by a von Frey hair, however useful in the scientific investigation of sensibility, is the most artificial of stimuli when compared with the normal stimulation of the body surface during the life of the organism. In these circumstances receptors of both cutaneous and subcutaneous situation must be excited simultaneously and in sequence, and from the extent of the surface stimulated and the moving passage of stimuli across that surface, constellations of sensory impulses must arise and, reaching the integrating centres together with impulses generated in proprioceptors, provide the material out of which the perception of spatial relationships is elaborated. It must also be remembered that while during sensory investigations under the conditions of experiment the body surface is still and passive, during normal activity it is a moving receptive surface that, as it were, goes out to meet cutaneous stimuli and thus receives the most complex combinations and permutations of sensory stimuli. The role of tactile, pressure and proprioceptive modes of sensibility is therefore far more complex than those of painful and thermal modes.

IX.—Summary.

In conclusion, lengthy as this review has been, it has not been possible within its scope to deal adequately with every aspect of the problem, or even to mention the contributions of all the numerous workers who have added to our knowledge. Nevertheless, it is hoped that the salient features of the subject have been presented.

From the many and diverse studies considered, certain conclusions seem to be emerging. The doctrine of specific nerve energy receives support from clinical, physiological and anatomical sources, but it is not the individual impulse that shows specific qualities, but rather the entire sensory pathway, for each mode of sensibility, along which pass the streams of nerve impulses. It is specific in a physiological as well as in an anatomical sense: specific in the morphology, selective excitability and other qualities of the end-organs: in the grouping together from peripheral origin to central destination of the fibres that carry the impulses for each sensory modality: in the fibre types involved—and this in turn involves some specificity in the impulse potentials and in the conduction rates and excit-

ability of the fibres: in the central excitatory states that modify each category of sensory impulse: and finally in the central destination of the impulses.

The long-established view that there are four primary modes of cutaneous sensibility, touch, pain, cold and warmth, also receives consistent support. Head's view that local sign in sensation and two-point discrimination are qualities inherent in the tactile impulse and are imposed by it on other modes of sensibility finds no support, and is incompatible with the results obtained in every field of research on sensory function.

Further, yet another conception is becoming clearer, namely, that of the physiological unit of sensory reception. Sherrington has shown that the physiological motor unit is the motor nerve cell and all the muscle fibres it supplies, some 150 or more. Reflex movement gradation is achieved by the fractionation of muscles into these groups. It seems that the unit of sensory function is similarly constituted: consisting of a posterior root fibre and all the end-organs (of a given mode of sensibility) that it innervates. Such a unit may reach macroscopic proportions, being disposed in the skin in area and in depth. Activation of a single "spot" within this unit influences every other spot within it. The unit's complexity is reflected in the fact that each group of end-organs (touch, pain, cold or warmth spots) receives its principal innervation from no less than two nerve fibres, and that each individual end-organ receives also an "accessory" innervation which appears to endow it with pain sensibility when supramaximally stimulated. Before this conception can be regarded as fully elucidated and confirmed much has yet to be learned, but it is one in harmony with what we know of the management of movement by the central nervous system. The view that end-organs have a selective excitability is reasonably established, and the accessory nerve supply of end-organs clears up some of the difficulty that this conclusion has previously presented.

Much of the obscurity surrounding the anatomy and physiology of the mechanism subserving pain has been removed by the work of Woollard and his pupils; work which constitutes one of the most striking advances in our knowledge of sensory function within recent years. When its biological implications are fully taken into account, and irrelevant standards of assessment abandoned, pain sensibility appears not to differ essentially from other modes of sensibility.

Problems of localization and discrimination of sensory stimuli promise to receive a large measure of solution in the light of what we are learning

of the nature of the physiological sensory unit, in which connection Tower's observations are of great significance.

On the negative side, it is clear that Head's theory of the morphological constitution of the afferent nervous system is invalid, and that Jackson's doctrine of release of function has proved singularly disappointing as a generalization of the observed facts of sensory loss from lesions of the nervous system. Possibly, it simply awaits a more penetrating application to these facts than it has yet received. Head's general theory is fatally handicapped by the attempted inclusion in it of a fallacious notion of the structure of the peripheral mechanisms of cutaneous sensibility. It attributes to simple conductors functions they cannot possibly subserve, and succumbs to the danger that always besets abstract thinking; that of confusing thoughts with things, of hypostatizing abstractions. Those familiar with Faber's "Nosography in Modern Internal Medicine" will recall how the progress of medical thought was held up in the early years of the last century by the prevalence of abstract thinking and the false analogies it engendered. Further, Head's theory embodies views on the evolution of structure and function in the nervous system that find neither internal nor external corroboration, and are indeed incompatible with all we know of this evolution. Nevertheless, when all that is speculative and abstract is removed from Head's contributions to this subject, there remains a most impressive body of observation that must have permanent value and will serve as the material for a more realist interpretation.

Running as a recurrent theme through many of the writings on cutaneous sensibility we find a tendency, uniformly unfortunate in its results, to postulate anatomical structures without taking the steps necessary to establish whether or not they exist. Head's protopathic and epicritic fibres, Lewis's nocifensor nerves, and the hypothetical dual system of pain fibres for the conducting of the different sensory qualities of pain, all come to grief when they make contact with the hard facts of anatomy. Perhaps it is not the least of Woollard's services to science to have redressed the balance between anatomy and physiology in the study of sensory function.

With the increasing range and complexity of experimental methods, workers in the different fields inevitably show signs of isolation from each other's thought and of a lack of sound orientation in the general field of sensory function. The mass of literature that the past few years has provided has tended, also, to a neglect of the fundamentally important work on sensation of the closing years of the last century. The maximal exploitation of original observation in any single department of the general

field can be attained only by those who are familiar with the results of research, old as well as new, in other departments. It is in connection with Trotter's contributions that this reflection seems most pertinent. To anyone who is actively thinking on the problems of cutaneous sensibility they are full of stimulating thought and of sane realism. Thus, his surmise as to the basis of sensory hypoæsthesia, and his findings on the selective excitability of nerve fibres foreshadow the work of Woollard and the observations of the electro-physiologists. It seems likely, also, that his views on the insulation of the nervous system and on the peculiar structure of the pain nerve-endings may throw light on the abnormal patterns of innervation and the abnormal subjective sensory symptoms (e.g. causalgia) that may ensue upon peripheral nerve lesions.

We have become too prone to regard the nervous system as a kind of ideal structure immune from the pathological reactions to damage that all other somatic tissues show, and thus as giving us a license to speculative and abstract thinking about it that we would be wary of in respect of any other tissue.

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Notices of Recent Publications

Epilepsy and Cortical Localization. By W. Penfield and T. C. Erickson. Baltimore: Charles C. Thomas. 1941. Pp. 623.

The authors have produced a volume of over 600 pages in which every aspect of epilepsy is dealt with, but what lends their book its peculiar value is the account it contains of their cortical stimulation experiments and of their studies of the atrophic and expanding local cerebral lesions that may give rise to epileptic fits.

Their studies on motor cortical representation in man are the fruit of stimulation experiments on a large number of subjects. Their results harmonize remarkably with those of Sherrington and Leyton on the higher apes, and they provide a map of the topographical representation of movements in the human cortex that will probably become the generally accepted one. This is particularly valuable because Foerster's familiar map represented large areas of the cortex as characteristically yielding movements on electrical stimulation, and suggested to the critical reader of his results that excessive currents had been employed and that the conclusions drawn were not likely to stand. This impression is amply confirmed by Penfield's work.

The statement, familiar to readers of neurological textbooks, that the pyramidal tract "arises primarily in the giant pyramidal cells of Area 4" will, it may be hoped, be modified in future editions since it is now known that only about 3 per cent. of pyramidal fibres arise from "giant" cells and that the cells so-called do not represent a physiological group, but only the largest members of a much more numerous group of pyramidal cells.

It is doubtful, also, whether we can subscribe to the statement that "consciousness" is "localized" in a "moderately discrete area of the brain" which the authors appear to believe is in the diencephalon; "the highest level of integration of the nervous system." For Sherrington—to whom the authors dedicate their volume—as for all other physiologists, this highest level is the cerebral cortex, the "roof brain," which, as Sherrington points out in his Gifford lectures, is indicated by a dozen different lines of evidence as being—in the language of metaphor—the "seat" of the mind and thus of consciousness.

The description of the different varieties of local epileptogenic lesion is excellent and the methods of dealing with them will prove of great value to the neurosurgeon, and of interest to the pathologist. Yet, as presented, the evidence of the role of local cortical lesions in the production of epileptic fits scarcely justifies the reader in believing that these lesions are of any considerable importance when the whole field of epilepsy is taken into account. The proportion of epileptic subjects whose fits are due to such lesions must be small indeed. Further, since of the 165 cases of the kind operated upon by the authors only 25 subsequently remained wholly free from fits, it would be unwise to expect too much from the surgical treatment of these lesions. Medication must still be the mainstay in the treatment of epilepsy.

In discussing the general aspects of idiopathic epilepsy, the authors are on less familiar ground, and their conception of epilepsy is so broad as to lack the definition

essential to any useful term in the grammar of medicine. Thus, local twitchings of abdominal and spinal muscles in a case of spinal cord glioma is spoken of as "spinal epilepsy," though Brown-Sequard's conception of a spinal epilepsy has long since been exploded by Graham Brown. Twitching of facial muscles in a case of 8th nerve fibroma is spoken of as a discharge from the facial nucleus: an access of vertigo and diplopia in another case of the same lesion as "brief epileptic discharge from the oculomotor nucleus," while an attack of yawning lasting for some hours becomes an "autonomic seizure." Even the urinary incontinence and foaming at the mouth of the epileptic fit are given this unnecessary interpretation. If all these diverse phenomena are to be called epileptic, then the term has lost all meaning. It is doubful, also, whether the categories of "bulbar," "decerebrate," "postural" and "diéncephalic" seizure have the reality the authors attribute to them.

In short, the reader may regret that the authors have not confined their exposition to the aspects of the problem within their own special experience and to those notable contributions they have made to it.

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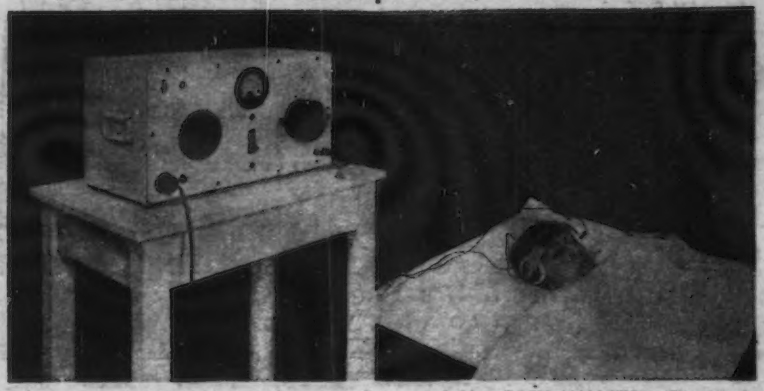

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